(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 436 005 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **29.03.95** (51) Int. Cl.[6]: **A61K 51/08**

(21) Application number: **90911595.8**

(22) Date of filing: **12.07.90**

(86) International application number:
PCT/EP90/01169

(87) International publication number:
WO 91/01144 (07.02.91 91/04)

(54) **LABELED POLYPEPTIDE DERIVATIVES.**

(30) Priority: **20.07.89 GB 8916597**
26.02.90 GB 9004258
09.03.90 GB 9005295

(43) Date of publication of application:
10.07.91 Bulletin 91/28

(45) Publication of the grant of the patent:
29.03.95 Bulletin 95/13

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 103 558
EP-A- 0 243 929
EP-A- 0 259 904
WO-A-89/02752
WO-A-90/03798

Merck Index 1983 No 4866

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EP 0 436 005 B1

Chemical Abstracts, vol. 113, no. 17, 1990, (Columbus, Ohio, US), D.R. Bard etal.: "Targeting of a chelating dervative of a short-chain analog of alpha-melanocyte stimulating hormone to Cloudman S91 melanomas", see abstract 148106m

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Description

The present invention relates to polypeptides, a process for their production, their use as a pharmaceutical, e.g. for treatment of tumors or as in vivo diagnostic agents, and to novel intermediates therefor.

Over the years the presence of various receptors has been demonstrated in a variety of tumors. Diagnostic agents therefor often have no clearly defined structure. Thus radioiodinated proteins or monoclonal antibodies having been reacted with chelating agents are randomly substituted. EP-A2-103,558 describes a method for in vitro quantitative determination of a biospecific affinity reaction, e.g. a homogenous immunological determination of insulin by conjugating aminophenyl -EDTA-Eu to insulin and measuring the fluorescence. There is no indication on the attachment site to insulin. EP-A2-243,929 discloses proteins or polypeptides conjugated to a reporter group via an intermediate grouping containing at least one radical of the formula -C(R) = N- or -CH(R)-NH- wherein R is hydrogen or an optionally substituted hydrocarbon residue, without solving the problem of random substitution on the protein or polypeptide. There thus exists a need for a new chemical approach to provide defined structures for use as diagnostic agents or for carrying radionuclides to tumors.

The present invention provides new labeled peptides useful in therapeutic and in vivo diagnostic applications.

According to the invention, there is provided a biologically active peptide selected from the group consisting of growth factors, peptide hormones, e.g. as indicated hereinafter, interferons and cytokines, e.g. IL-1, IL-4 or IL-6, and analogous or derivatives thereof and bearing at least one chelating group linked to an amino group of said peptide, the chelating group being capable of complexing a detectable element and such amino group having no significant binding affinity to target receptors.

These compounds are referred to thereafter as LIGANDS OF THE INVENTION. They possess at least one chelating group capable of reacting with a detectable element, e.g. a radionuclide, a radio-opaque element or a paramagnetic ion, to form a complex and further are capable of binding to receptors which are expressed or overexpressed by tumors or metastases. The chelating group is attached to an amino group of the peptide which is not involved in receptor binding. Such amino group with the attached chelating group does not significantly interfere with or prevent receptor binding of the peptide. Preferably said amino group is not directly attached to an aromatic residue.

The term receptors is used therein to cover also proto-oncogenes, e.g. HER-2/neu proto-oncogene (also known as c-erb B2) or EGFR (also known as c-erb B1) which are overexpressed e.g. in breast or ovarian cancer tumors.

According to the invention the chelating group may be attached either directly or indirectly by means of a divalent bridging group to the amino group of the peptide.

The term biologically active peptides is used therein to cover natural peptides isolated from nature or fermentation of cells, e.g. produced through genetic engineering, or synthesized and also their derivatives or analogues.

By derivatives and analogues is understood in particular natural peptides, wherein one or more amino acid units have been omitted and/or replaced by one or more other amino acid radical(s) and/or wherein one or more functional groups have been replaced by one or more other functional groups and/or wherein one or more groups have been replaced by one or several other isosteric groups. In general, the term covers all derivatives of a biologically active peptide which exhibit a qualitatively similar effect to that of the unmodified peptide. They may be for example more potent than the naturally occurring peptide. The term also covers antagonists to the naturally occurring peptide.

Preferably the biologically active peptide is of 3 or more than 3 amino-acids, in one or several linked chains. It is understood that the term biologically active peptide does not include antibody or immunoglobulin molecules.

Suitable examples of growth factor peptides include epidermal growth factor (EGF), insulin-like growth factors (IGF-I and IGF-II), fibroblast growth factor (FGF), tumor necrosis factor (TNF), transforming growth factor (TGF-α and TGF-βn), platelet derived growth factor (PDGF), nerve growth factor, bombesin and analogues or derivatives thereof.

Suitable examples of hormonal peptides include insulin, LHRH, gastrin, gastrin releasing peptide, thyrotropin releasing hormone (TRH), thyroid stimulating hormone (TSH), prolactin, vasoactive intestinal polypeptide (VIP), angiotensin and analogues or derivatives thereof. Examples of cytokines are IL-1, IL-2, IL-4 and IL-6.

In a further or alternative embodiment, the present invention provides:

a. Epidermal growth factor (EGF may be of various origin, e.g. mouse EGF, rat EGF, human EGF);

b. Insulin-like growth factor (IGF), particularly IGF-1 (Somatomedin C);

c. LHRH, LHRH agonists or LHRH antagonists;
d. Gastrin;
e. Gastrin releasing peptide;
f. Bombesin or bombesin antagonists;
g. Transforming growth factors, particularly TGF-α;
h. Platelet derived growth factor;
i. Angiotensin;
j. Thyroid stimulating hormone;
k. Vasoactive intestinal polypeptide;
l. Fibroblast growth factor;
m. Prolactin;
n. Thyrotropin releasing hormone;
o. Insulin;
p. Tumor necrosis factor;
q. Nerve growth factor;
r. IL-1, IL-2, IL-4 or IL-6, preferably IL-1, IL-4 or IL-6;
s. Interferons

and derivatives and analogues thereof

each of (a) to (s) bearing at least one chelating group linked to an amino group thereof, which amino group does not significantly participate in receptor binding and the chelating group being capable of complexing a detectable element.

In a series of specific or alternative embodiments, the present invention provides:

A. a peptide selected from any of the groups of peptides (a) to (q) as defined above and derivatives and analogues thereof each of (a) to (q) bearing at least one chelating group linked to an amino group of said peptide, which amino group does not significantly participate in receptor binding and the chelating group being capable of complexing a detectable element;

B. a peptide selected from any of the groups of peptides (a) to (l) as defined above and derivatives and analogues thereof each of (a) to (l) bearing at least one chelating group linked to an amino group of said peptide, which amino group does not significantly participate in receptor binding and the chelating group being capable of complexing a detectable element;

C. a peptide selected from any of the groups of peptides (a) to (k) as defined above and derivatives and analogues thereof each of (a) to (k) bearing at least one chelating group linked to an amino group of said peptide, which amino group does not significantly participate in receptor binding and the chelating group being capable of complexing a detectable element;

D. a peptide selected from any of the groups of peptides (a) to (g) as defined above and derivatives and analogues thereof each of (a) to (g) bearing at least one chelating group linked to an amino group of said peptide, which amino group does not significantly participate in receptor binding and the chelating group being capable of complexing a detectable element.

More particularly preferred peptides are EGF, LHRH, LHRH agonists, LHRH antagonists and bombesin antagonists.

The chelating group or groups present in the LIGAND OF THE INVENTION are linked covalently to the amino group of the peptide. Preferably the chelating group or groups present in the LIGAND OF THE INVENTION are attached, whether directly or indirectly, by an amide bond to the amino group of the peptide.

Preferably the LIGANDS OF THE INVENTION bear one chelating group.

According to the invention the chelating group may be attached either to a side chain amino group of the peptide, e.g to the N^{ε}-amino group of a lysine, and/or to a terminal N-amino group of the peptide (referred to herein as N^{α}-amino group), with the proviso that such amino group whether side chain or N^{α}-attached does not significantly interfere with or impair the binding affinity of the peptide to the target receptors.

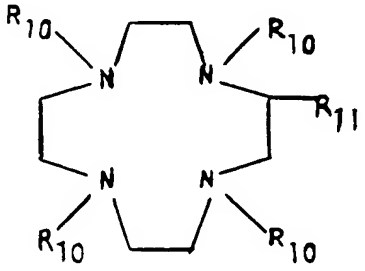
Among the peptides listed above, the following may preferably bear a chelating group on the N^{α}-amino group: EGF, IGF-1, gastrin, gastrin releasing peptide, insulin, TGF-α, LHRH, bombesin, VIP, and analogues or derivatives thereof. Peptides which bear at least one chelating group attached to a side chain amino group preferably may be: an EGF comprising at least one lysine in its amino-acid sequence, e.g. hEGF, LHRH, LHRH agonists, LHRH antagonists, IGF-1, gastrin, gastrin releasing peptide, bombesin antagonists, VIP, and analogues or derivatives thereof.

A group of peptides comprises those wherein one lysine is present. Another group of peptides comprises those wherein more than one lysine group is present. A further group of peptides comprises

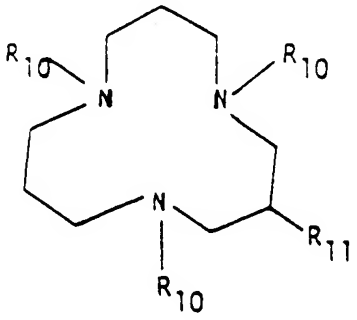
those free of lysine.

As it will be appreciated when the peptide bears a terminal amino group which is substituted or protected, e.g. by acyl, the substituting or protecting group may conveniently be removed prior to the coupling with the chelating group or bridging group.

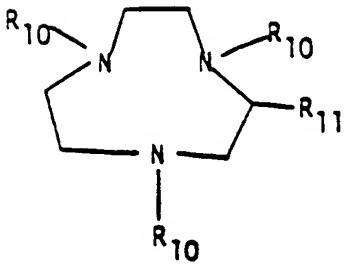
Suitable chelating groups are physiologically acceptable chelating groups capable of complexing a detectable element. Preferably the chelating group has substantially a hydrophilic character. Examples of chelating groups include e.g. iminodicarboxylic groups, polyaminopolycarboxylic groups, e.g. those derived from non cyclic ligands e.g. ethylene diaminetetraacetic acid (EDTA), diethylene triamine pentaacetic acid (DTPA), N-hydroxyethyl-N,N',N'-ethylene diaminetriacetic acid (HEDTA), ethylene glycol-O,O'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)ethylenediamine-N,N'-diacetic acid (HBED) and triethylenetetramine hexaacetic acid (TTHA), those derived from substituted EDTA or -DTPA, those derived from macrocyclic ligands, e.g. 1,4,7,10-tetra-azacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), C-functionalised tetraazacyclododecane-tetra-acetic acids, tetraazacyclotetradecane-tetra-acetic acids, triazacyclododecane triacetic acids and triazacyclononane triacetic acids, for example chelating groups derived from compounds of formula Ia, Ib or Ic,



(Ia)



(Ib)

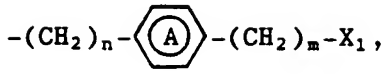


(Ic)

wherein

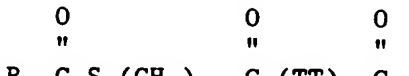
R_{10} is $-CH_2COOH$ or a functional derivative thereof, e.g. an ester, and

R_{11} is -Alk-X_1 or

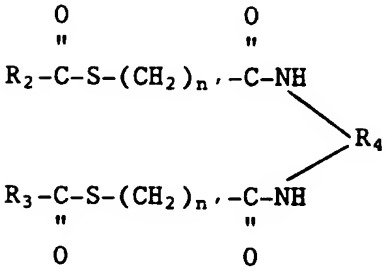


wherein each of n and m independently is 0, 1, 2 or 3, Alk is C_{1-11}alkylene, X_1 is -NCS or NH_2 optionally substituted by a protecting group and ring A is substituted or unsubstituted,

those derived from N-substituted or C-substituted macrocyclic amines including also cyclames, e.g. as disclosed in EP 304, 780 A1 and in WO 89/01476-A, groups of formula IIa or IIb,



(IIa)

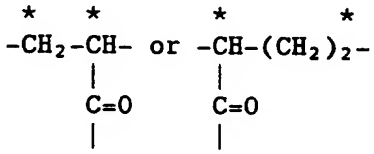


(IIb)

wherein

each of R_1, R_2 and R_3 independently is C_{1-6}alkyl, C_{6-8}aryl or C_{7-9}arylalkyl, each optionally substituted by OH, C_{1-4}alkoxy, COOH or SO_3H,

R_4 is



wherein the carbon atoms marked with * are attached to the imino groups,

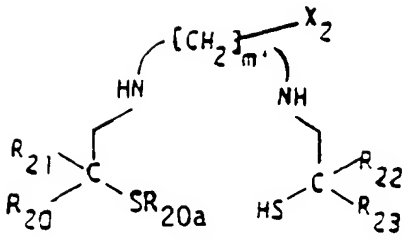
n' is 1 or 2,

i is an integer from 2 to 6, and

TT are independently α or β amino acids linked to each other by amide bonds,

e.g. as disclosed in EP 247,866 A1

groups derived from bis-aminothiol derivatives, e.g. compounds of formula III



(III)

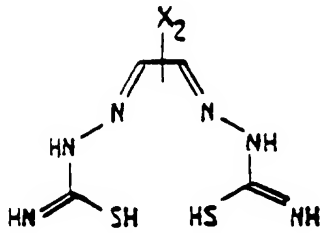
wherein

each of R_{20}, R_{20a}, R_{21}, R_{22} and R_{23} independently is hydrogen or C_{1-4}alkyl,

X_2 is either a group capable of reacting with the N-amino group of the peptide, or a group capable of binding with the divalent bridging group and

m' is 2 or 3,

groups derived from dithiasemicarbazone derivatives, e.g. compounds of formula IV

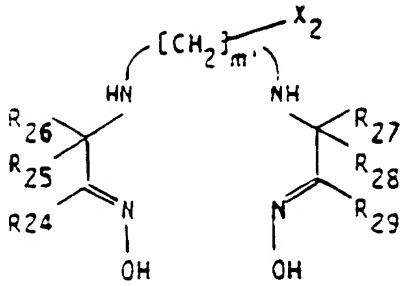


(IV)

wherein

X_2 is as defined above,

groups derived from propylene amine oxime derivatives, e.g. compounds of formula V

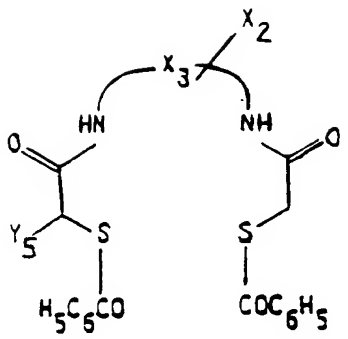


(V)

wherein

each of R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and R_{29} independently are hydrogen or C_{1-4}alkyl, and

X_2 and m' are as defined above, groups derived from diamide dimercaptides, e.g. compounds of formula VI



(VI)

wherein

X_2 is as defined above,

X_3 is C_{1-4}alkylene, C_{1-4}alkylene substituted by one or two CO_2R_{30}, by CH_2COR_{30}, $CONH_2$ or $CONHCH_2CO_2R_{30}$, phenylene, or phenylene substituted by CO_2R_{30} wherein R_{30} is C_{1-4}alkyl, and

Y_5 is hydrogen or CO_2R_{30},

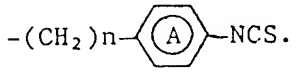
groups derived from porphyrins, e.g. N-benzyl-5,10,15,20-tetrakis-(4-carboxyphenyl)porphine or TPP bearing a group X_2 as defined above, or from Desferal (Deferoxamine), the chelating group being other than EDTA or substituted EDTA when the peptide is insulin.

Aryl is preferably phenyl. Arylalkyl is preferably benzyl.

Alkylene may be straight chain or branched, preferably straight chain.

Examples of X_2 include radicals of formula $-(X_4)_{n''}-X_5$ wherein X_4 is C_{1-6}alkylene; C_{1-6}alkylene optionally attached to the carbon atom by an oxygen atom or -NH- or phenyl-C_{1-3}alkyl; n'' is 0 or 1 and X_5 is -NCS, -NCO, or a carboxy group or a functional derivative thereof, e.g. acid halide, anhydride or hydrazide. When X_4 is phenyl-C_{1-3}alkyl, X_5 is preferably in para. For example X_2 can be -O-$(CH_2)_{2-6}$-COOH or a functional derivative thereof, or p-isothiocyanato-benzyl or -phenethyl.

In compounds of formula Ia, Ib or Ic R_{11} is preferably Alk-NCS or



Preferably Alk is C_{1-6}alkylene, more preferably C_{1-4}alkylene, n is preferably 1 or 2. Ring A is preferably unsubstituted.

In compounds of formula III, R_{20a} is preferably hydrogen.

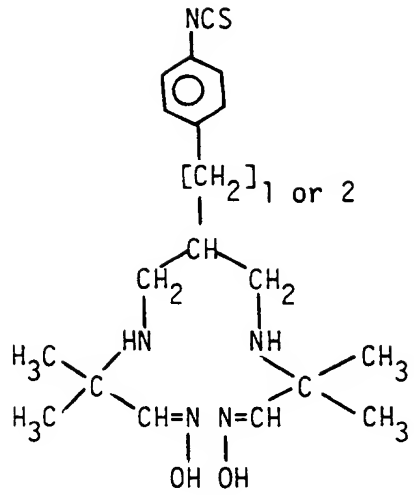
In compounds of formula V, R_{24} and/or R_{29} are preferably hydrogen. Each of R_{25} to R_{28} independently is preferably methyl. More preferably R_{25} to R_{28} are each methyl. m' is preferably 3. When m' is 3, X_2 is preferably located in position 2.

X_2 is preferably p-isothiocyanato-benzyl or p-isothiocyanato-phenethyl.

Particularly preferred chelating groups are those derived from

- EDTA, DTPA, DOTA; or
- substituted EDTA or DTPA, e.g. N'-p-isothiocyanatobenzyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N'-p-isothiocyanatophenethyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N-{2-[bis-(carboxymethyl)amino]ethyl}-N'-{2-[bis(carboxymethyl)amino]-2-(p-isothiocyanatobenzyl)ethyl}-glycine or -(p-isothiocyanatophenethyl)-homologue; or
- substituted DOTA, e.g. a compound of formula Ia, or compounds of formula Ib or Ic, particularly those wherein R_{11} is $-(CH_2)_{1-6}$-NCS, p-isothiocyanatobenzyl or p-isothiocyanatophenethyl; or

- compound of formula Va



(Va)

As will be appreciated, where the chelating group present in the LIGAND OF THE INVENTION contains vicinal carboxylic acid groups, these may also be present as anhydride functional groups.

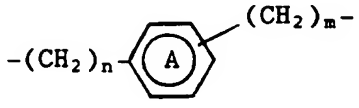
According to the invention when the chelating group is attached indirectly by means of a divalent bridging group or a spacer group to an amino group of the peptide, it may be linked for example through a group of formula (α_1)

-Z-R-CO- (α_1)

wherein

A is C_{1-11} alkylene, hydroxy substituted C_{2-11} alkylene, C_{2-11} alkenylene,

cyclohexylene, substituted cyclohexylene, or a radical of formula (α_2)



(α_2)

wherein n and m are as defined above,

the ring A is substituted or unsubstituted, and

R_5 is a residue as attached in Cα of a natural or synthetic α-amino acid, and

Z is a divalent group derived from a functional moiety capable of covalently reacting with the chelating agent.

Preferably A is C_{1-4} alkylene, -CH(R_5)- or a radical of formula (α_2) wherein ring A is unsubstituted.

In the radical of formula (α_2), the substituent -$(CH_2)_m$- is preferably located in meta or para, more preferably in para.

Z may be for example a group which can form an ether, ester or amide bonding with the chelating group. Z is preferably -CO- or -NH-, more preferably -NH-.

When Z is -CO-, the divalent bridging group of formula (α_1) may be a divalent radical derived from a dicarboxylic acid.

Examples of significances for R_5 include e.g. hydrogen, C_{1-11}alkyl, benzyl, substituted benzyl, e.g. substituted on the phenyl ring by hydroxy, halogen, C_{1-3}alkyl or C_{1-3}alkoxy, and -CH_2-naphthyl.

A group of preferred LIGANDS OF THE INVENTION are the compounds of formula X

$$A - Z_1 - B \qquad (X)$$

wherein

A is a chelating group, for example a chelating group derived from a chelating agent comprising a reactive carboxy or amino group or a functional derivative thereof,

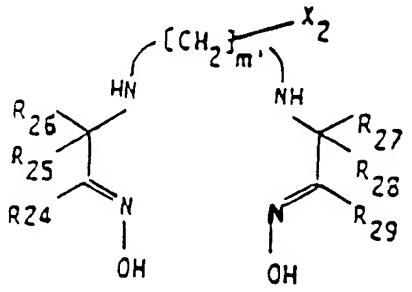
Z_1 is a direct bond or a divalent bridging group, and

B is a biologically active peptide, preferably a peptide (a) to (s) or an analogue or derivative thereof as defined above,

the moiety A-Z_1- being attached to an amino group of B having no significant binding affinity to target receptors.

Preferred compounds of formula X are those wherein:

A is a chelating group derived from N'-p-isothiocyanatobenzyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N'-p-isothiocyanatophenethyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N-{2-[bis-(carboxymethyl)amino]ethyl}-N'-{2-[bis(carboxymethyl)amino]-2-(p-isothiocyanatobenzyl)-ethyl}-glycine, DOTA, C-functionalised tetraazacyclododecane-tetraacetic acids, C-functionalised tetraazacyclotetradecane-tetraacetic acids, C-functionalised triazacyclododecane triacetic acids, C-functionalised triazacyclononane triacetic acids, preferably compounds of formula Ia, Ib or Ic, particularly compounds of formula Ia, Ib or Ic wherein R_{11} is -$(CH_2)_{1-6}$-NCS, p-isothiocyanatobenzyl or p-isothiocyanatophenethyl, or from a compound of formula V



(V)

wherein

R_{24} to R_{29} and m' are as defined above,

and

X_2 is p-isothiocyanato-benzyl or -phenethyl; or

Z_1 is a direct bond or a group of formula α_1 wherein the -CO- group is attached to the amino group of the peptide and Z is -NH-; or

B is EGF, LHRH, a LHRH agonist, a LHRH antagonist, bombesin or a bombesin antagonist.

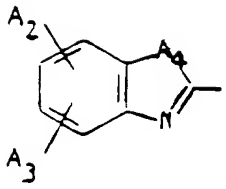
Examples of LHRH antagonists are compounds of formula VII

$$R_{33} - A_1 - B_1 - C_1 - D_1 - E_1 - F_1 - G_1 - H_1 - I_1 - K_1 - NH_2 \qquad (VII)$$

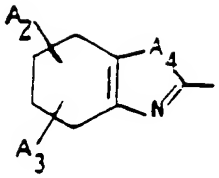
wherein

R_{33} is hydrogen, C_{1-7}acyl or carbamoyl,

A_1 is D-Phe optionally substituted in the phenyl ring by halogen, CF_3, C_{1-3}alkyl and/or C_{1-3}alkoxy, α- or β-naphthyl-D-alanine, D-Trp optionally substituted in 5 or 6 position by halogen or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, D- or L- Pro, D- or L-3,4-dehydroproline, D- or L-Ser, D- or L-Thr, D- or L-Ala, D-pyroglutamine, 3-(9-anthryl)-D,L-alanyl, 3-(2-fluorenyl)-D,L-alanyl or 3-(Het)-D,L-alanyl wherein Het is a heterocyclic aryl radical selected from



or



wherein

A_2 and A_3 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, chlorine and bromine, and A_4 is O, S or N

B_1 is D-Phe optionally substituted in the phenyl ring by halogen, NO_2, C_{1-3}alkyl or C_{1-3}alkoxy, D-α-methylPhe optionally substituted in 4 position by chlorine, 2,2-diphenylglycine or 3-(2-naphthyl)-D-alanine,

C_1 is D-Trp optionally substituted in 5 or 6 position by halogen, NO_2 or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, 3-(2- or 1-(naphthyl)-D-alanine, 3-D-pyridylalanine, D-Tyr, D-Phe optionally substituted by halogen, C_{1-3}alkyl and/or C_{1-3}alkoxy, D-3-Pz-Ala, D-Tin-Glu or D-Nic-Lys,

D_1 is L-Ser,

E_1 is Tyr, Phe optionally substituted in the phenyl ring by halogen, C_{1-3}alkyl and/or C_{1-3}alkoxy, Orn, Lys, Lys-Nic, MPic-Lys, Pic-Lys, DPic-Lys, MPic-Lys, DMG-Lys, Pmc-Lys, Pzc-Lys, PmACAla, PzACAla, His, Dpo, Arg, 3-(3-pyridyl)-Ala, Trp, N-(3-pyridyl)acetyl-Lys or Glu(pMeO-phenyl), Cit, HOBLys or PzACAla,

F_1 is D-Phe optionally substituted in the phenyl ring by halogen, NO_2, NH_2, C_{1-3}alkyl or C_{1-3}alkoxy, D-Trp optionally substituted in 5 or 6 position by halogen, NO_2 and/or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, 3-(2-naphthyl)-L-alanyl, D-Tyr, D-Orn, D-Lys, D-Lys-Nic, D-MNic-Lys, D-MPic-Lys, Pic-Lys, DPic-Lys, D-Pmc-Lys, D-Pzc-Lys, D-Bz-Lys, D-lLys, AnGlu, D-NACAla, D-PzACAla, D-PmACAla, D-3-(3-pyridyl)-Ala, D-His (subst. H or benzyl), D-Arg, D-homo-Arg(Et_2), D-Cit, D-HCi, D-Lys-Pic, D-Cit(C_{1-3}-alkyl), D-HCi(C_{1-3}alkyl), D-Glu(AA) or α-amino-ω-ureido-C_{2-4}alkanoic acid,

G_1 is Leu, Nle, Nval, N-α-methylLeu, Trp, Phe, Met, Tyr, Val, Ile, alloIle, Abu or Ala,

H_1 is Arg, lOrn, Lys, lLys or Cyp-Lys

I_1 is Pro, hydroxyproline, 3,4-dehydroproline, Pip and

K_1 is D-Ala, D-Leu, Gly, D-Ser or Sar,

in free form or in salt form.

The chelating group or groups may be attached to the terminal N^{α}-amino group in position 1 when R_{33} is hydrogen and/or to the free amino groups present in E_1 and/or F_1 and/or H_1 of formula VII. Preferably the LIGANDS OF THE INVENTION of the LHRH antagonist series are compounds of formula VII comprising a chelating group attached to the amino group in position 1 or 6 or 8, particularly 6 or 8.

Examples of LHRH agonists are compounds of formula VIII

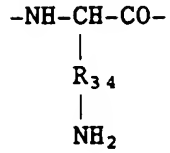
pGlu-His-A_5-Ser-B_2-C_2-D_2-Arg-Pro-E_2 (VIII)

in which

A_5 is Trp, Phe or 3-(1-naphthyl)Ala,

B_2 is Tyr, Phe D-Trp, or 3-(pentafluorophenyl)Ala,

C_2 is an amino-acid unit of formula



wherein R_{34} is $-(CH_2)_{p'}-$, $-(CH_2)_{p'}-CO-$, $-(CH_2)_{p'''}-R_{35}-$ or $-(CH_2)_{p'''}-Y_6-(CH_2)_{p'''}-$, wherein p' is 1 to 5,

p'' is 0 or 1 to 3, each of p''' independently is 1 to 3, R_{35} is phenyl or cyclohexyl and Y_6 is O, S, -SO- or SO_2,

D_2 is Leu, Ile, Nle, MeLeu, and

E_2 is Gly-NH_2, -NH-R_{31} or -NH-NH-CO-NH-R_{32} wherein R_{31} is hydrogen, lower alkyl, cycloalkyl or fluoro lower alkyl and R_{32} is hydrogen or lower alkyl,

in free form or in salt form.

The residue C_2 has preferably the D-configuration.

The chelating group is preferably attached to the free amino group present in C_2.

Examples of bombesin antagonists are compounds e.g. as disclosed in EP 339,193 A and EP 315,367 A, the contents of which being herein incorporated by reference, particularly compounds of formula IXa

$$\underset{}{R_{36}} - \underset{1}{A_6} - \underset{2}{B_3} - \underset{3}{C_3} - \underset{4}{D_3} - \underset{5}{E_3} - \underset{6}{F_3} - \underset{7}{G_3} - \underset{8}{H_3} - \underset{9}{I_3} - \underset{10}{Q} \qquad \text{(IXa)}$$

wherein

R_{36} is hydrogen, C_{1-6}alkyl, C_{2-6}alkanoyl, C_{4-6}cycloalkoxycarbonyl or C_{1-4}alkoxycarbonyl,

A_6 is a direct bond or Gly, Arg, Lys, Phe, Asp, Nal, Pro, β-Ala or Glp,

B_3 is a direct bond or Gly, Pro or Asn,

C_3 is a direct bond or Lys or D-Nal,

D_3 is a direct bond or His, MeHis, EtHis, PrHis, Gln, Glu (OMe)-Glp, Leu, MeLeu, Lys, Pal, Phe, Pro, Arg, Trp or Thr,

E_3 is Trp, Val, Nal, Leu, Lys, Pal,

F_3 is Ala, MeAla, Aib, Gly, Pro, Leu, Phe, Ser, Val, Nal, Thr, Arg or Glu,

G_3 is Val, Aib, Leu, Ile, Thr, Phe or Ser,

H_3 is Gly, Sar, Ala, Ser, Aib, Pro, Lys, Asp, Arg, Val, Ac^3c, Ac^5c or Ac^6c,

I_3 is His, MeHis, Aib, Val, Leu, MeLeu, Ala, Ile, Met, Pro, Phe, Gln, Lys, Pal, Ser, Thr, Glu, Asp, Trp or Nal, and

Q is K_3-R_{37} wherein K_3 is Leu, MeLeu, Ile, MeIle, Aib, Pro, Val, MeVal, Phe, Ape, MeApe, Met, Ser, Gln, Glu or Trp and R_{37} is C_{1-3}alkylamino, C_{1-4}(dialkyl)amino or C_{1-3}alkoxy or Q is C_{1-6}alkoxy, C_{1-10}alkylamino or C_{1-10}(dialkyl)amino,

and compounds of formula IXb

$$\underset{1}{A_7} - \underset{2}{B_4} - \underset{3}{Gln} - \underset{4}{Trp} - \underset{5}{Ala} - \underset{6}{Val} - \underset{7}{W} - \underset{8}{X_6} - \underset{9}{Y_6} - \underset{10}{T_1} \qquad \text{(IXb)}$$

wherein

A_7 is hydrogen, Boc, Lys, Arg,

B_4 is a direct bond or Asn, Thr, Glp,

W is Gly or Ala,

X_6 is a direct bond, His(R_{38}), Phe, Ser or Ala,

Y_6 is a direct bond, Leu or Phe,

T_1 is amino, $NH(CH_2)_4CH_3$, benzylamino, Met-R_{39}, Leu-R_{39}, Ile-R_{39}, Ile-R_{39} or Nle-R_{39},

R_{38} is hydrogen or benzyl, and

R_{39} is amino, hydroxy, methoxy or -$NHNH_2$,

in free form or in salt form.

Preferably the LIGANDS OF THE INVENTION of the bombesin antagonist series are compounds of formula IXa or IXb comprising a chelating group attached to the free amino group or groups when present in position 1, and/or 2 and/or 4 and/or 5, and/or 6 and/or 7 and/or 8, more preferably only one chelating group attached as indicated above.

The LIGANDS OF THE INVENTION may exist e.g. in free or salt form. Salts include acid addition salts with e.g. organic acids, polymeric acids or inorganic acids, for example hydrochlorides and acetates, and salt forms obtainable with the carboxylic or sulphonic acid groups present in the chelating group, e.g. alkali metal salts such as sodium or potassium, or substituted or unsubstituted ammonium salts.

The present invention also includes a process for the production of the LIGANDS OF THE INVENTION, comprising

a) removing at least one protecting group which is present in a peptide bearing a chelating group, or

b) linking together by an amide bond two peptide fragments each of them containing at least one amino acid in protected or unprotected form and one of them containing the chelating group, wherein the amide bond is in such a way that the desired amino acid sequence is obtained, and then effecting optionally stage a) of the process, or

c) linking together a chelating agent and the desired peptide in protected or unprotected form in such a way that the chelating group is fixed on the desired amino group of the peptide, and then effecting optionally stage a), or

d) removing a functional group of an unprotected or a protected peptide bearing a chelating group or converting it into another functional group so that another unprotected or a protected peptide bearing a chelating group is obtained and in the latter case effecting stage a) of the process,

and recovering the LIGAND thus obtained in free form or in salt form.

The above reactions may be effected in analogy with known methods, e.g. as described in the following examples, in particular process a). When the chelating group is attached by an ether, ester or amide bond, this may be carried out analogously to the methods used for ether, ester or amide formation respectively. Where desired, in these reactions, protecting groups which are suitable for use in peptides or for the desired chelating groups may be used for functional groups which do not participate in the reaction. The term protecting group may also include a polymer resin having functional groups.

In the above process steps b) and c), when it is desired to produce a peptide in which the chelating group is attached by means of a divalent bridging or spacer group to the amino group of the peptide, the bridging group may be present on the corresponding amino-acids, peptide fragments or peptides used as starting material, or attached to the chelating group. Said amino-acids, peptide fragments or peptides may be prepared by reacting in analogy with known methods the corresponding amino-acids or peptides free of bridging or spacer group with a corresponding bridging or spacer-yielding compound, for example an acid of formula HO-CO-R-COOH, H_2N-R-COOH or a reactive acid derivative thereof such as an active ester. Examples of active ester groups or carboxy activating groups are e.g. 4-nitrophenyl, pentachlorophenyl, pentafluorophenyl, succinimidyl or 1-hydroxy-benzotriazolyl.

Alternatively the chelating agent may first be reacted with a bridging or spacer group-yielding compound, in order to bear the bridging or spacer group and then be reacted in analogy with known methods with the peptide, peptide fragment or amino-acid. According to a preferred embodiment of the invention, when the chelating group is derived from a polyamino polycarboxylic compound, the chelating agent, e.g. EDTA- or DTPA-dianhydride, is reacted with the bridging or spacer-group yielding compound, e.g. H_2N-R-COOH or a reactive acid derivative thereof, for example an alkyl ester thereof, to yield the chelating agent modified by the bridging group. This compound may then be activated, e.g. converted into the corresponding hydrazide by reaction of the modified chelating agent with e.g. hydrazine hydrate. The hydrazide chelating agent may then be reacted with the amino-acid, peptide fragment or peptide in analogy with known methods, e.g. via azide coupling after conversion into the corresponding azide.

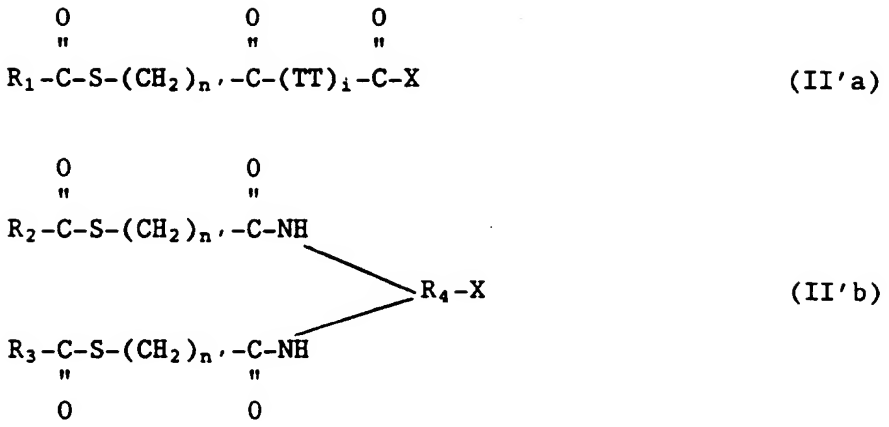
According to a further preferred embodiement of the invention, when it is desired to link a chelating agent bearing a carboxylic function, e.g. -COOH or an anhydride thereof, directly to the amino group of the peptide (in the absence of a divalent bridging or spacer group), the chelating agent may be activated, e.g. converted into the corresponding hydrazide by reaction with e.g. hydrazine hydrate. The hydrazide chelating agent may then be reacted with the amino-acid, peptide fragment or peptide in analogy with known methods, e.g. via azide coupling after conversion into the corresponding azide.

When it is desired to attach the chelating group to the terminal N-amino group of a peptide or peptide fragment used as starting material, and which comprises one or more side chain amino groups, these side chain amino groups are conveniently protected with a protecting group, e.g. as used in peptide chemistry.

When it is desired to attach the chelating group on a side chain amino group of a peptide or peptide fragment used as starting material, and the peptide comprises a free terminal amino group, the latter may be protected with a protecting group.

When it is desired to attach the chelating group on the terminal amino group of a peptide or peptide fragment used as starting material, and said terminal amino group is substituted or in a protected form, e.g. substituted by acyl, the substituting or protecting group may conveniently be removed prior to the coupling with the chelating group.

The chelating groups of formula IIa or IIb may be linked to a peptide by reacting a chelating agent of formula II'a or II'b,



(II'a)

(II'b)

wherein X is an activating group capable of forming an amide bond. The reaction may be performed as disclosed e.g. in EP 247,866 A1.

The chelating agent used in process step b) or c) may be known or prepared in analogy with known procedures.

The LIGANDS OF THE INVENTION may be purified in conventional manner, e.g. by chromatography. Preferably the LIGANDS OF THE INVENTION contain less than 5% by weight of peptides free of chelating groups.

In a further embodiment the present invention also provides the LIGANDS OF THE INVENTION as defined above which are complexed with a detectable element (hereinafter referred to as CHELATES OF THE INVENTION), in free form or in salt form, their preparation and their use for in vivo diagnostic and therapeutic treatment.

The CHELATES OF THE INVENTION comprise each LIGAND OF THE INVENTION, particularly as mentioned in (a) to (s) above, complexed with a detectable element.

In a series of specific or alternative embodiement, the present invention provides also the groups of LIGANDS as specified in (A) to (D) above complexed with a detectable element.

By detectable element is meant any element, preferably a metal ion which exhibits a property useful in therapeutic or in vivo diagnostic techniques, e.g. emission of a detectable radiation or an influence on NMR relaxation properties.

Suitable detectable metal ions include for example heavy elements or rare earth ions, e.g. as used in CAT scanning (Computer axial tomography), paramagnetic ions, e.g. Gd^{3+}, Fe^{3+}, Mn^{2+} and Cr^{2+}, fluorescent ions, e.g. Eu^{3+}, and radionuclides, e.g. γ-emitting radionuclides, β-emitting radionuclides, α-emitting radionuclides, positron-emitting radionuclides e.g. ^{68}Ga, ^{62}Cu, ^{52}Fe and ^{62}Zn and Auger-electron-emitting radionuclides.

Suitable γ-emitting radionuclides include those which are useful in diagnostic techniques. The γ-emitting radionuclides advantageously have a half-life of from 1 hour to 40 days, preferably from 5 hours to 4 days, more preferably from 12 hours to 3 days. Examples are radionuclides derived from Gallium, Indium, Technetium, Ytterbium, Rhenium and Thallium e.g. ^{67}Ga, ^{111}In, ^{99m}Tc, ^{169}Yb and ^{186}Re. Preferably the γ-radionuclide is selected depending on the metabolism of the selected LIGAND OF THE INVENTION or the peptide used. More preferably the LIGAND OF THE INVENTION is chelated with a γ-radionuclide having a half-life corresponding to or longer than the half-life of the peptide on the tumor.

Further radionuclides suitable for use in imaging are positron-emitting radionuclides, e.g. as mentioned above.

Suitable β-emitting radionuclides include those which are useful in therapeutic applications, for example those derived from ^{90}Y, ^{67}-Cu, ^{186}Re, ^{188}Re, ^{169}Er, ^{121}Sn, ^{127}Te, ^{143}Pr, ^{198}Au, ^{109}Pd, ^{165}Dy, ^{32}P, ^{142}Pr or Ag. The β-radionuclide advantageously have a half-life of from 1 hr to 14.3 days, preferably from 2.3 to 100 hrs. Preferably the β-emitting radionuclide is selected in order to have a half-life corresponding to or longer than the half-life of the peptide on the tumor.

Suitable α-emitting radionuclides are those which are used in therapeutic treatments, e.g. ^{211}At, ^{212}Bi.

Further radionuclides suitable for therapeutic treatment are Auger-electron-emitting radionuclides, e.g. ^{125}I, ^{123}I, ^{77}Br.

The CHELATES OF THE INVENTION may be prepared by reacting the LIGAND with a corresponding detectable element yielding compound, e.g. a metal salt, preferably a water-soluble salt. The reaction may be carried out by analogy with known methods, e.g. as disclosed in Perrin, Organic Ligand, Chemical Data Series 22. NY Pergamon Press (1982); in Krejcarit and Tucker, Biophys. Biochem. Res. Co:. 77: 581 (1977) and in Wagner and Welch, J. Nucl. Med. 20: 428 (1979).

The CHELATE may conveniently be formed by reacting the LIGAND with the detectable element yielding compound at a pH at which the LIGAND OF THE INVENTION is chemically stable.

The detectable metal ion may also be provided to the solution as a complex with an intermediate chelating agent, e.g. a chelating agent which forms a chelate complex that renders the metal ion soluble but is less thermodynamically stable than the CHELATE. Example of such an intermediate chelating agent is 4,5-dihydroxy-1,3-benzene-disulfonic acid (Tiron). In such a process, the detectable metal ion exchanges the ligand.

The CHELATES OF THE INVENTION may also be produced by linking together covalently a chelating agent complexed with the detectable element, and the peptide in protected or unprotected form and if desired removing at least one protecting group which is present. The same reaction may be performed using a chelating agent complexed with a metal ion and then in the resulting complexed peptide the metal ion may be replaced by the desired detectable element.

The CHELATES OF THE INVENTION may also be produced by linking together a chelating agent complexed with the detectable element, and a peptide fragment comprising at least one amino acid in protected or unprotected form and then continuing the peptide synthesis step by step until the final peptide sequence is obtained and if desired removing at least one protecting group which is present. Instead of the detectable element the chelating agent may be complexed with a non detectable metal and this metal may then be replaced by the detectable element in the resulting complexed peptide.

According to the invention the chelating group may be attached through a bridging or spacer group, e.g. a radical of formula (α_1) as defined above; in such a case it is meant in the above process steps for preparing the CHELATES OF THE INVENTION that either the peptide or peptide fragment or the chelating agent may bear said bridging or spacer group.

The above mentioned reactions may be effected in analogy to known methods. Depending on the chelating group present, the labeling efficiency may approach 100% so that purification is not required. Radionuclides such as for example Technetium-99m may be used in oxidized form, e.g. Tc-99m pertechnetate, which may be complexed under reducing conditions.

The above mentioned reactions are conveniently effected under conditions avoiding trace metal contamination. Preferably distilled de-ionized water, ultrapure reagents, chelation-grade radioactivity etc..are used to reduce the effects of trace metal.

The CHELATES OF THE INVENTION may exist e.g. in free or salt form. Salts include acid addition salts with e.g. organic acids, polymeric acids or inorganic acids, for example hydrochlorides and acetates, and salt forms obtainable with the carboxylic acid groups present in the molecule which do not participate to the chelate formation, e.g. alkali metal salts such as sodium or potassium, or substituted or unsubstituted ammonium salts.

Particularly preferred CHELATES OF THE INVENTION are:

- compounds of formula X wherein A is a chelating group derived from a compound of formula Va, said compounds of formula X being complexed with radioactive Tc, e.g. ^{99m}Tc;
- compounds of formula X wherein A is a chelating group derived from a compound of formula Ia, Ib or Ic wherein R_{11} is -$(CH_2)_{1-6}$-NCS, p-isothiocyanatobenzyl or p-isothiocyanatophenethyl, said compounds of formula X being complexed with radioactive Yttrium, e.g. ^{90}Y;
- compounds of formula X wherein A is a chelating group derived from N'-p-isothiocyanatobenzyl-diethylene triamine-N,N,N'',N''-tetraacetic acid or N'-p-isothiocyanatophenethyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, said compounds of formula X being complexed with Europium;
- compounds of formula X wherein A is a chelating group derived from N-{2-bis(carboxymethyl)amino]-ethyl}-N'-{2-[bis(carboxymethyl)amino]2-(p-isothiocyanatobenzyl)-ethyl}-glycine, said compounds being complexed with radioactive Indium or Yttrium, e.g. ^{90}Y or ^{111}In.

The CHELATES OF THE INVENTION and their pharmaceutical acceptable salts exhibit pharmaceutical activity and are therefore useful depending on the detectable metal ion either as an imaging agent, e.g. visualisation of receptor-positive tumors and metastases when complexed with a paramagnetic, a γ-emitting metal ion or a positron-emitting radionuclide, or as a radiopharmaceutical for the treatment in vivo of receptor-positive tumors and metastases when complexed with a α- or β-radionuclide or an Auger-electron-emitting radionuclide, as indicated by standard tests, e.g. showing a biodistribution as indicated in Example 12 on i.v. administration of from about 1 to 5 μg/kg of LIGAND labeled with 0.5 to 2 mCi ^{111}In. The

CHELATES OF THE INVENTION also possess affinity for receptors expressed or overexpressed by tumors and metastases, as indicated in standard in vitro binding assays, e.g. as described in Example 11, the CHELATES being preferably added at a concentration of about 10^{-10} to 10^{-8} M.

In a series of specific or alternative embodiments, the present invention also provides:

1. A method for in vivo imaging, e.g. in vivo detection of tumors or metastases in a subject which comprises a) administering a CHELATE OF THE INVENTION to said subject and b) recording the localisation of the tissues, e.g. tumors or metastases, targeted by said CHELATE.

This method of the invention is particularly useful for the in vivo detection of tumors which express or overexpress receptors, more particularly at a high incidence on tumorigenic cells. CHELATES OF THE INVENTION for use in the in vivo detection method of the invention are the CHELATES which are complexed with a γ-emitting radionuclide, a positron-emitting radionuclide or a paramagnetic metal ion, e.g. as indicated above.

The CHELATES OF THE INVENTION for use as an imaging agent in method (1) may be administered parenterally, preferably intravenously, e.g. in the form of injectable solutions or suspensions, preferably in a single injection. An appropriate dosage will of course vary depending upon, for example, the LIGAND and the type of detectable element used, e.g. the radionuclide. A suitable dose to be injected is in the range to enable imaging by photoscanning procedures known in the art. When a radiolabeled CHELATE OF THE INVENTION is used, it may advantageously be administered in a dose having a radioactivity of from 0.1 to 50 mCi, preferably 0.1 to 30 mCi, more preferably 0.1 to 20 mCi.

In animals an indicated dosage range may be of from 0.1 to 10 μg/kg of LIGAND labeled with 0.1 to 2 mCi γ-emitting radionuclide, e.g. ^{111}In. In larger mammals, for example humans, an indicated dosage range may be of from 1 to 200 μg LIGAND labeled with 0.1 to 15 mCi, preferably 0.1 to 30 mCi, e.g. 3 to 15 mCi, γ-emitting radionuclide, depending on the γ-emitting radionuclide used. For example with In, it is preferred to use a radioactivity in the ower range, whereas with Tc, it is preferred to use a radioactivity in the upper range.

The enrichment in the tumorigenic sites with the CHELATES may be followed by the corresponding imaging techniques, e.g. using nuclear medicine imaging instrumentation, for example a scanner, γ-camera , rotating γ-camera, each preferably computer assisted; PET-scanner (Positron emission tomography); MRI equipment or CAT scanning equipment.

2. A method for in vivo treatment of tumors and metastases in a subject in need of such a treatment which comprises administering to said subject a therapeutically effective amount of a CHELATE OF THE INVENTION.

CHELATES OF THE INVENTION for use in the in vivo treatment method of the invention are the CHELATES complexed with a α-, β- or Auger-electron-emitting radionuclide as defined above.

The method of the invention is particularly useful for in vivo treatment of tumors which express or overexpress receptors, more particularly at a high incidence on tumorigenic cells.

Dosages employed in practising the therapeutic method of the present invention will of course vary depending e.g. on the particular condition to be treated, for example the volume of the tumor, the particular CHELATE employed, for example the half-life of the CHELATE in the tumor, and the therapy desired. In general, the dose is calculated on the basis of radioactivity distribution to each organ and on observed target uptake. For example the CHELATE may be administered at a daily dosage range having a radioactivity of from 0.1 to 3 mCi/kg body weight, e.g. 1 to 3 mCi, preferably 1 to 1.5 mCi/kg body weight.

In animals an indicated dosage range may be of from 0.1 to 5 μg/kg of LIGAND labeled with 0.1 to 3 mCi α- or β-emitting radionuclide, e.g. ^{90}Y. In larger mammals, for example humans, an indicated dosage range is of from 1 to 200 μg LIGAND labeled with 0.1 to 3 mCi/kg body weight, e.g. 0.1 to 1.5 mCi/kg body weight α- or β-emitting radionuclide, conveniently administered in divided doses up to 4 times a day.

The α- or β-emitting CHELATES OF THE INVENTION may be administered by any conventional route, in particular parenterally, e.g. in the form of injectable solutions or suspensions. They may also be administered advantageously by infusion, e.g. an infusion of 30 to 60 min. Depending on the site of the tumor, they may be administered as close as possible to the tumor site, e.g. by means of a catheter. The mode of administration selected may depend on the dissociation rate of the CHELATE used and the excretion rate.

The CHELATES OF THE INVENTION may be administered in free form or in pharmaceutically acceptable form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

The CHELATES OF THE INVENTION for use in the method of the present invention may preferably be prepared shortly before the administration to a subject, i.e. the labeling with the desired detectable metal ion, particularly the desired α-, β- or γ-radionuclide, may be performed shortly before the administration.

The CHELATES OF THE INVENTION may be suitable for imaging or treating various types of solid or non-solid tumors and metastases thereof, e.g. pituitary, gastroenteropancreatic, central nervous system, brain, breast, ovarian, colonic, prostate, kidney or lung cancer, paragangliomas, neuroblastomas, gliomas, medullary thyroid carcinomas, myelomas, bone tumors, carcinoids etc and metastases thereof.

For these uses, it is advantageous to choose, as the polypeptide moiety, such a compound as specifically accumulates at a particular organ or tissue of diagnostic or therapeutic target. According to the invention receptor-specific LIGANDS and CHELATES may be obtained for targetting a defined cell population.

According to a further aspect of the invention, there is provided:

i. a pharmaceutical composition comprising a LIGAND OF THE INVENTION in free or in pharmaceutically acceptable salt form, together with one or more pharmaceutically acceptable carriers or diluents therefor;

ii. a pharmaceutical composition comprising a CHELATE according to the invention in free or in pharmaceutically acceptable salt form, together with one or more pharmaceutically acceptable carriers or diluents therefor.

iii. use of a LIGAND OF THE INVENTION in free or in pharmaceutically acceptable salt form, in the preparation of a diagnostic agent for imaging target tissues.

Such compositions may be manufactured in conventional manner. Preferably they are in liquid forms.

A composition according to the invention may also be presented in separate package with instructions for mixing the LIGAND with the metal ion and for the administration of the resulting CHELATE. It may also be presented in twin-pack form, that is, as a single package containing separate unit dosages of the LIGAND and the detectable metal ion with instructions for mixing them and for administration of the CHELATE. A diluent or carrier may be present in the unit dosage forms.

According to a further embodiment of the invention, compounds of formula XI

$$A - Z - R - Z_2 \qquad (XI)$$

wherein
A, Z and R are as defined above, and

Z_2 is COOH or a functional group of a carboxy function, e.g. (C_{1-12}alkoxy) carbonyl

are new and form part of the invention.

Preferred compounds of formula XI are those wherein A is derived from EDTA, DTPA or DOTA, particularly DTPA. Z is preferably -NH-. R is preferably C_{1-4}alkylene, particularly ethylene, -CH(R_5)- as defined above or a radical of formula (α_2) wherein ring A is unsubstituted.

Compounds of formula XI may be prepared in accordance with known methods. For example a polyamino polycarboxylic chelating agent may be reacted, preferably in the form of a dianhydride, with the bridging or spacer-yielding compound in an aqueous medium. The pH may conveniently be adjusted to slightly acidic.

Compounds of formula XII

$$A - Z'_1 - CO - X_7 \qquad (XII)$$

wherein
A is as defined above,
Z'_1 is either a direct bond or -Z-R- wherein Z and R are as defined above, and
X_7 is -NH-NH_2 in protected or unprotected form or -N_3,
are also novel and form part of the invention.

Preferably each of A, Z and R independently has one of the preferred significances as indicated above, respectively.

Compounds of formula XII may be prepared in accordance with known methods. They may be prepared by reacting either a compound of formula XI or a chelating agent bearing a rective -COOH or a functional derivative thereof with hydrazine or a derivative thereof and then converted into the corresponding azide, e.g. as disclosed thereafter. Hydrazine is preferably used with one amino group being in protected form. The reaction may conveniently be performed in water or in a mixture of water and an alcohol, e.g.

methanol, at a moderate temperature such as between cooling and slight heating, for example at room temperature, e.g. for one hour to 30 hours. If required the compounds of formula XII may be isolated and purified using any known purification methods such as chromatography.

In the following examples, all temperatures are in ° C and $[\alpha]_D^{20}$ -values uncorrected. The following abbreviations are employed:

Boc = tert.-butoxycarbonyl
TFA = trifluoroacetic acid
DTPA = diethylenetriamine-pentaacetic acid
DMF = dimethyl formamide

The factor "F" shows the peptide content in the products obtained (F = 1 conforms with 100 % peptide content). The difference up to 100 % [(1-1/F) x 100] consists of acetic acid and water.

EXAMPLE 1: DTPA - NH - CH_2 - CH_2 $COOCH_3$

5g sodium bicarbonate and 2.1g H_2N-CH_2-CH_2-CO-OCH_3, HCl are dissolved in 30 l water. After addition of 5.3g DTPA-dianhydride and after 1 min reaction time the pH of the mixture is adjusted to 3 with HCl and then to 5.5 with NaOH 1N. The resulting mixture is freeze dried and then purified by chromatography eluting first with a mixture 7/4/2 and then with a mixture 7/5/4 of chloroform/methanol/50% acetic acid, to yield the title compound.

MH^+: 479 (FAB-MS)

EXAMPLE 2: DTPA - NH - CH_2 - CH_2 - CO - $NHNH_2$

200 mg hydrazine hydrate are added to a methanolic solution of 330 mg DTPA-NH-CH_2-CH_2-CO-OCH_3. After 24 hours at room temperature, the methanol is evaporated and the residue is chromatographied on silica gel using as eluant a mixture of 5/8/3 chloroform/glacial acetic acid/water. The resulting product is further purified on an ion exchange resin (AG 4-X4, OH-Form; Biorad). The title compound is obtained as a white lyophilisate.

MH^+: 479 (FAB-MS)

EXAMPLE 3: DTPA - β - Ala - mEGF

a) Preparation of the azide

14.3 mg DTPA-β-Ala-hydrazide are dissolved in 1 ml DMF and cooled to -15 °C. 0.02 ml 3N HCl in diethylether and 5.4 µl tert.-butyl nitrite are then added to this solution. After 30 minutes, the resulting solution can be used for the next step (mother-liquor contains 0.03 mMol azide/ml solution).

b) Coupling

3 mg mEGF (1-53) are dissolved in 1 ml DMF and cooled to 0 °C. To this solution are added 0.88 µl N-ethyl diisopropylamine and then 25 µl of the solution obtained in a). The resulting mixture is allowed to stay for 16 hours in the refrigerator. The progress of the reaction is tested by thin layer chromatography (eluant: 7/5/4 of chloroform/methanol/50% acetic acid) and further 0.88 µl N-ethyl diisopropylamine and 25 µl azide solution obtained in a) are added to the mixture. After a further period of 12 hours in the refrigerator, the mixture is evaporated in vacuo and the residue is purified by reversed phase HPLC (column: ET 250/8/4 NUCLEOSIL 300-7 C18; Macherey and Nagel).

F = 0.91

Amino acid analysis:	Th.	Found
ASX	7	7,1
GLX	3	3,2
SER	6	5,3
HIS	1	0,9
THR	2	1,6
beta-ALA	1	1,1
ARG	4	4,0 (Standard)
TYR	5	5,1
CYS-CYS	6	3,2
VAL	2	1,8
MET	1	1,3
ILE	2	2,2
LEU	4	4,4
PRO	2	1,9

EXAMPLE 4: ^{111}In labeled DTPA-β-Ala-mEGF

1 mg DTPA-β-Ala-mEGF is dissolved in 0.01 M acetic acid. The resulting solution is passed through a 0.22 µ Millex-GV filter. $^{111}InCl_3$ Amersham, 370 MBq/ml) is prediluted in an equal volume of 0.5 M sodium acetate. Labeling is carried out by mixing DTPA-β-Ala-mEGF with the $InCl_3$ solution and gentle mixing at room temperature.

EXAMPLE 5: ^{90}Y labeled DTPA-β-Ala-mEGF

^{90}Y is obtained from a ^{90}Sr-^{90}Y radionuclide generator. The construction of the generator, its elution and the conversion of the [^{90}Y]EDTA to the acetate complex are performed in accordance with the method disclosed by M.Chinol and D.J. Hnatowich in J. Nucl. Med. 28, 1465-1470 (1987). 1 mg of DTPA-β-Ala-mEGF dissolved in 5ml 0.01M acetic acid is allowed to warm to room temperature and 1.0 mCi of ^{90}Y in 50 µl sterile 0.5M acetate is added. The mixture is then left undisturbed for 30 min to 1 hr to maximize chelation.

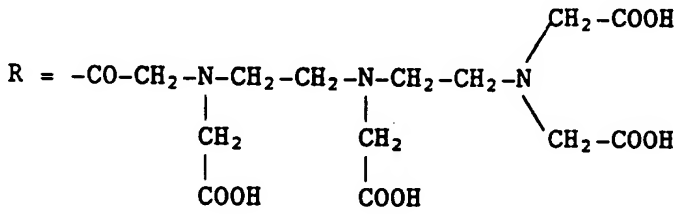
EXAMPLE 6: [DTPA-β-Ala-Trp^{14}]-Tetragastrin

By following the procedure of Example 3 (preparation of the azide and coupling) but using H-Trp-Met-Asp-Phe-NH_2 instead of mEGF, the title compound is obtained.
$[\alpha]_D^{20}$ = -6,7° (c = 0.5 in 95% AcOH) F = 0.77
The title compound is then labeled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

EXAMPLE 7: [DTPA-β-Ala-Phe^{B1}]-bInsuline

By following the procedure of Example 3 but using A^1,B^{29}-Di-Boc-Insuline instead of mEGF and removing the protecting group with 100% CF_3COOH according to known method, the title compound is obtained.
F = 0.83
The title compound is then labeled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

EXAMPLE 8: Acetyl-DPhe(pCl)-DPhe(pCl)-DTrp-Ser-Tyr-Dlys(R)-Leu-Arg-Pro-DAla-NH_2



150 mg DTPA-hydrazide in 25 ml DMF are cooled to -20°. To this mixture are added 0.37 ml 3N HCl in ether and then 72 µl t.-butyl nitrite and the resulting mixture is stirred for ca. 30 min while the temperature is maintained from -15° to -20°. Thereafter a solution of 200 mg of acetyl-DPhe(pCl)-DPhe(pCl)-DTrp-Ser-Tyr-DLys-Leu-Arg-Pro-DAla-NH_2 in 100 ml DMF cooled to -20° is added followed by the addition of N-ethyl-diisopropylamine until pH 9 is obtained. The resulting mixture is stirred for ca. 70 hours at 0° while keeping the pH at 9.

DMF is then removed in vacuo until a final volume of 5 ml is left and the title compound is precipitated by addition of ether. The precipitate is filtered, washed and dried.

For purification, the title compound is dissolved in 150 ml water, the solution is adjusted to pH 7 by addition of NH_4OH, adsorbed on a duolite ES 881 column and eluted using a gradient of H_2O-Dioxane-AcOH. The fractions containing the title compound are collected and then lyophilized.

$[\alpha]_D^{20}$ = -14.5° (c = 0.2 in 95% AcOH)

The starting compounds may be prepared as follows:

a. **DTPA-Hydrazide**

2g sodium bicarbonate are dissolved in 7 l water. To this solution are added 0.74 g BocHN-NH_2 and then 2 g DTPA dianhydride. After a few seconds a clear solution is obtained. The mixture is then evaporated at 40° to a volume of 0.5 l which is adjusted to pH 5 (max.) with 1N HCl. After stirring for 15 minutes, the mixture is adjusted to pH 7 with 1N NaOH and then lyophilized. Thereafter the product is chromatographied on silica gel using as eluant a mixture of chloroform, methanol, water and AcOH. The monosubstituted product is collected and further purified on an ion exchange resin (AG 4-X4, OH-Form; Biorad). The resulting product is dissolved in 10 ml TFA, the mixture is stirred for 30 minutes. DTPA-hydrazide is precipitated by addition of diisopropyl ether, filtered and dried under high vacuo.

b. **Acetyl-DPhe(pCl)-DPhe(pCl)-DTrp-Ser-Tyr-Dlys-Leu-Arg-Pro-DAla-NH_2**

This peptide is synthesized on a mild acid cleavable resin [e.g. 4-(2',4'-dimethoxyphenyl-aminomethyl)-phenoxymethyl-polystyrene, 1% crosslinked; available from e.g. Novabiochem] using N-α-Fmoc protected aminoacids which are added in the following order:

Fmoc-DAla-OH → Fmoc-Pro-OH → Fmoc-Arg(Pmc)-OH → Fmoc-Leu-OH →
Fmoc-DLys(Boc)-OH → Fmoc-Tyr(tBu)-OH → Fmoc-Ser(tBu)-OH →
Fmoc-DTrp-OH → Fmoc-DPhe(pCl)-OH → Fmoc-DPhe(pCl)-OH

In each cycle the aminoacids are activated with diisopropyl-carbodiimide/HOBt in DMF and, after complete coupling, the Fmoc-groups cleaved with 20% piperidine in DMF. N-acetylation in the last step is performed with acetic acid anhydride.

The protected peptide-resin is treated with TFA/H_2O (95:5) in order to simultaneously remove side chain protecting groups and liberate the peptide. Purification is achieved with RP-HPLC followed by ion-exchange on AG-4X4, acetate. The title compound is thus obtained.

The title compound is then labeled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

EXAMPLE 9: DTPA-DNal-(2)^1-DPhe(p-Cl)-DTrp-Ser-Tyr-DLys(CH$_2$-CHOH-CH$_2$OH)-Leu-Lys(CH$_2$-CHOH-CH$_2$OH)-Pro-DAla-NH$_2$

By following the procedure of Example 8 (preparation of the azide and coupling) but using H-DNal(2)^1-DPhe(p-Cl)-DTrp-Ser-Tyr-Dlys(CH$_2$-CHOH-CH$_2$OH)-Leu-Lys(CH$_2$-CHOH-CH$_2$OH)-Pro-DAla-NH$_2$ as starting material, the title compound is obtained.

F = 0.83

The starting peptide may be prepared by the solid phase synthesis procedure, e.g. as disclosed in Example 8b, but using Fmoc-DLys(CH$_2$-CHOH-CH$_2$OH) in cycles 3 and 5, Fmoc-DNal-OH is used in the last cycle. After complete coupling the protected peptide-resin is treated with TFA/H$_2$O (95:5) in order to simultaneously remove side chain protecting groups and liberate the peptide. The peptide is purified by RP-HPLC followed by ion-exchange on AG-4X4, acetate.

$[\alpha]_D^{20}$ = - 16 ° (c = 0.5 in 95 % AcOH)

The title compound is then labelled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

EXAMPLE 10: Acetyl-His-Trp-Ala-Val-DAla-Lys(β-Ala-DTPA)-Leu-OEt

By following the procedure of Example 3 (preparation of the azide and coupling) but using Acetyl-His-Trp-Ala-Val-DAla-Lys-Leu-OEt as starting material, the title compound is obtained.

The starting peptide may be prepared as disclosed in EP-315 367-A.

The title compound is then labelled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

The affinity of the CHELATES OF THE INVENTION to the receptors present in the tumors may be assayed as follows:

EXAMPLE 11: BINDING PROPERTIES

An EGF receptor positive human tumor is removed and immediately stored at -70 °C. During the subsequent isolation procedure this material is kept at 0 to 4 °C. The tumor tissue is dissected into small cubes prior to homogenisation in 5 parts of Buffer A (20 mM HEPES, 0.1 mM EDTA and 250 mM sucrose, pH 7.4). Membranes are isolated by differential centrifugation. The material is then diluted in the incubation buffer containing 30 mM HEPES, pH 7.4, 1mg/ml BSA and 1 mM benzamidine. The test mixture (200 µl final volume) contains 100 000cpm [^{125}I]-EGF, the tissue (5 to 25 µg protein/assay) and compound of Example 3 at a concentration of 10^{-9}M. After mixing the icecold test solution on a vortex the tubes (polypropylene) are transfered to a waterbath and incubated for 30 min at 37 °C. The reaction is stopped by addition of icecold Hank's or Tris buffer (4ml). The Tris buffer contains 10 mM Tris in 0.9% sodium chloride solution and is adjusted to pH 7.4. Routinely, filtration buffers contain 1% BSA (Fraction V) to suppress non-specific binding to the glass fiber filters (type A/E) that have been soaked in the filtration buffer a few minutes prior to use. The tubes are rinsed with 4 ml of the filtration buffer and the rinsing fluid is put over the respective filters. A third wash of the filters is followed by drying and the measurement of the filter-bound radioactivity in a γ-counter. The washing of the filters takes approximately 10 sec. It is observed that compound of Example 3 inhibits specifically bound [^{125}I]-EGF (IC_{50} = 1.3 nM).

A similar binding assay procedure is repeated but using 1 µg of the compound of Example 3 labelled with 0.2 mCi $^{111}InCl_3$ as test substance. The tests are performed in siliconized borosilicate glass tubes and controls containing additionally 10^{-7} M EGF to determine non-specific binding are used. In these assays it is observed that the compound of Example 4 binds with high affinity to the EGF-receptors (IC_{50} = 3 nM).

By following a similar binding assay procedure but using LHRH receptor positive anterior pituitary membranes from male Sprague-Dawley rats, 1 µg of the compound of Example 8 labelled with 0.4 mCi $^{111}InCl_3$ (labelling performed at room temperature for 15 minutes) and 10^{-6} M (DAla^6)LHRH for the

determination of the non-specific binding, it is observed that ^{111}In labelled compound of Example 8 binds with high affinity to the LHRH-receptors (IC_{50} = 1.1 nM).

EXAMPLE 12: BIODISTRIBUTION

Biodistribution of radioactivity may be determined either with standard imaging techniques in nude mice weighing 20 + 5 g and bearing an EGF receptor positive tumour (MDA 231, MDA 468 or A 431 tumors) or through serial sacrifice of a number of such animals and determination of the organ radioactivity. Compound of Example 4 is administered i.v. to the animals at a dosage corresponding to 90-100μCi and the radioactivity is assessed 5 min, 10 min, 15 min, 30 min, 60 min, 20 hrs and 48 hrs. 5 minutes after injection, radioactivity is detected in the liver, kidneys, urinary bladder and in the tumor site. Radioactivity is increasing and is localized on the tumor site 60 min after injection.

EXAMPLE 13: DTPA-mEGF

By following the procedure of Example 8 but using mEGF as starting material, the title compound is obtained.

The title compound is then labelled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

EXAMPLE 14: 1-(p-isothiocyanatobenzyl)-DTPA-mEGF

To a solution of 3 mg of mEGF in 5 ml acetonitrile/water (1/1 v/v), which is adjusted to pH 9.8 with NA_2CO_3, 1,5 mg of N-{2-[bis(carboxymethyl)amino]ethyl}-N'-{2-bis-[bis(carboxymethyl)amino]-2-(p-isothiocyanato-benzyl)-ethyl}-glycine [or 1-(p-isothiocyanatobenzyl)-DTPA] are added. After a reaction time of 9 hours at room temperature the solution is diluted with water to 20 ml and loaded on to RP-HPLC column. The title compound is isolated by gradient elution (buffer A: 0.1% trifluoroacetic acid, buffer B: 0.1% trifluoroacetic acid in acetonitrile) and obtained as white lyophilisate after freeze drying.

The title compound is then labelled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

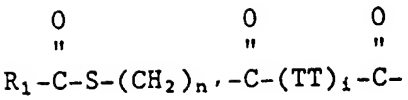
EXAMPLE 15: p-isothiocyanatobenzyl-DOTA-mEGF

The title compound is obtained according to the procedure of Example 14 using p-isothiocyanatobenzyl-DOTA instead of 1-(p-isothio-cyanatobenzyl)-DTPA.
The title compound is then labelled with ^{111}In or ^{90}Y according to the procedure of Example 4 or 5 respectively.

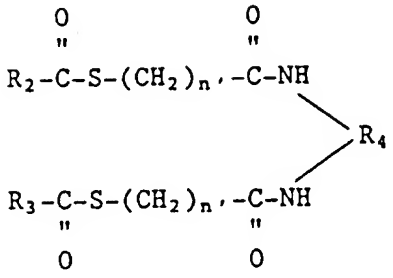
Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A ligand comprising a biologically active peptide selected from the group consisting of growth factors, insulin, LHRH, gastrin, gastrin releasing peptide, thyrotropin releasing hormone, thyroid stimulating hormone, prolactin, vasoactive intestinal peptide, angiotensin, interferons, IL-1, IL-4 and IL-6, and analogues or derivatives thereof and bearing at least one chelating group selected from polyamino polycarboxylic groups, a group of formula IIa or IIb,



(IIa)

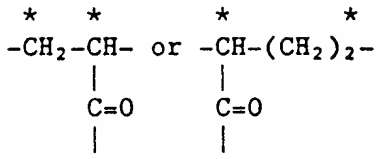


(IIb)

wherein

each of R_1, R_2 and R_3 independently is C_{1-6}alkyl, C_{6-8}aryl or C_{7-9}arylalkyl, each optionally substituted by OH, C_{1-4}alkoxy, COOH or SO_3H,

R_4 is



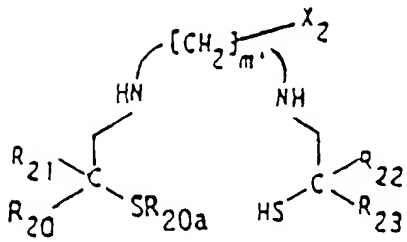
wherein the carbon atoms marked with * are attached to the imino groups,

n' is 1 or 2,

i is an integer from 2 to 6, and

TT are independently α or β amino acids linked to each other by amide bonds,

or a group derived from compounds of formula III



(III)

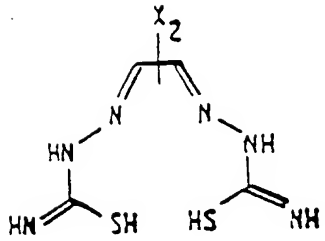
wherein

each of R_{20}, R_{20a}, R_{21}, R_{22} and R_{23} independently is hydrogen or C_{1-4}alkyl,

X_2 is either a group capable of reacting with the N-amino group of the peptide, or a group capable of binding with the divalent bridging group and

m' is 2 or 3,

from compounds of formula IV

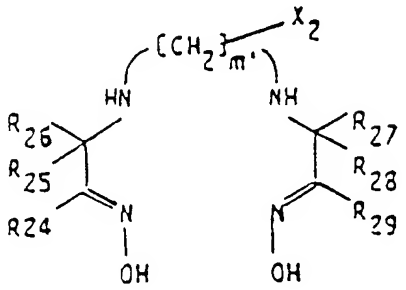


(IV)

wherein

X_2 is as defined above,

from compounds of formula V

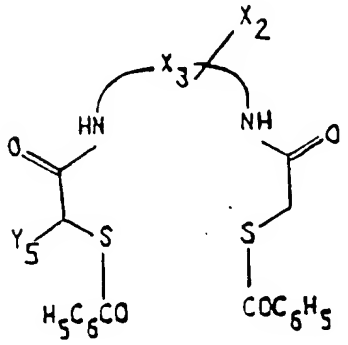


(V)

wherein

each of R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and R_{29} independently is hydrogen or C_{1-4}alkyl, and X_2 and m' are as defined above,

from compounds of formula VI



(VI)

wherein

X_2 is as defined above,

X_3 is C_{1-4}alkylene, C_{1-4}alkylene substituted by one or two CO_2R_{30}, by CH_2COR_{30}, $CONH_2$ or $CONHCH_2CO_2R_{30}$, phenylene, or phenylene substituted by CO_2R_{30} wherein R_{30} is C_{1-4}alkyl, and

Y_5 is hydrogen or CO_2R_{30},

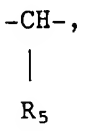
from porphyrins or from Desferal,

the chelating group being linked either directly or indirectly by means of a divalent bridging group to an amino group of said peptide in such a way to form an amide bond, the divalent bridging group being a group of formula α_1

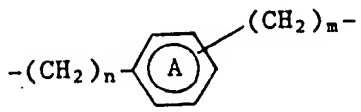
Z-R-CO- (α_1)

wherein

R is C_{1-11}alkylene, hydroxy substituted C_{2-11}alkylene, C_{2-11}alkenylene,



cyclohexylene, substituted cyclohexylene,
or a radical of formula (α_2)



(α_2)

wherein n and m are as defined above,
the ring A is substituted or unsubstituted, and

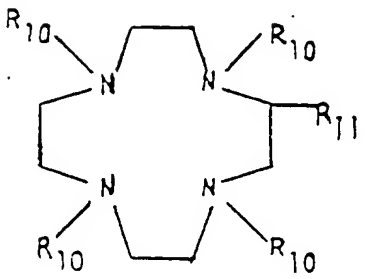
R_5 is a residue as attached in Cα of a natural or synthetic α-amino acid, and

Z is NH or CO, said amino group of the peptide being not directly attached to an aromatic residue,

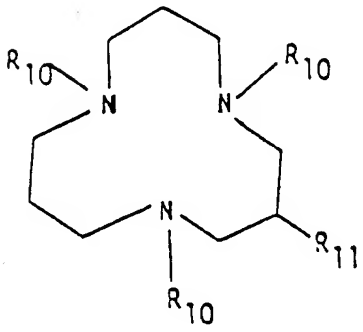
the chelating group being capable of complexing a detectable element and the amino group of said peptide having no significant binding affinity to target receptors, with the proviso that the chelating group is other than EDTA or substituted EDTA when the peptide is insulin,
in free form or in salt form.

2. A ligand according to claim 1 wherein the chelating group is a polyamino poly(acetic acid) group selected from a group derived from diethylene triamine pentaacetic acid (DTPA), N-hydroxyethyl-N,N',N'-ethylene diaminetriacetic acid (HEDTA), ethylene glycol-O,O'-bis(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)-ethylene-diamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), from substituted EDTA or -DTPA, from 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), the chelating group being other than substituted EDTA when the peptide is insulin.

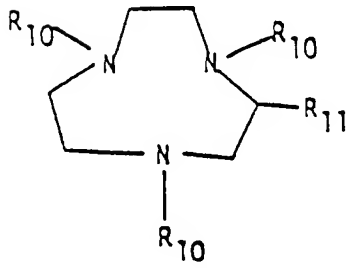
3. A ligand comprising a biologically active peptide selected from the group consisting of growth factors, insulin, LHRH, gastrin, gastrin releasing peptide, thyrotropin releasing hormone, thyroid stimulating hormone, prolactin, vasoactive intestinal peptide, angiotensin, interferons, IL-1, IL-4 and IL-6, and analogues or derivatives thereof and bearing at least one chelating group derived from N'-p-isothiocyanatobenzyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N'-p-isothiocyanatophenethyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N-{2-[bis(carboxymethyl)amino]ethyl}-N'-{2-[bis-(carboxymethyl)amino]-2-(p-isothiocyanatobenzyl)ethyl}-glycine, a compound of formula Ia, Ib or Ic,



(Ia)



(Ib)

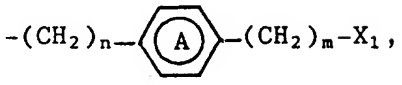


(Ic)

wherein

R_{10} is $-CH_2COOH$ or a functional derivative thereof, and

R_{11} is -Alk-X_1 or



wherein each of n and m independently is 0, 1, 2 or 3, Alk is C_{1-11}alkylene, X_1 is -NCS or NH_2 optionally substituted by a protecting group and ring A is substituted or unsubstituted, or a compound of formulae III to VI as defined in claim 1 wherein X_2 is $-(X_4)_{n''}-X_5$ wherein X_4 is C_{1-6}alkylene; C_{1-6}alkylene optionally attached to the carbon atom by an oxygen atom or -NH- or phenyl-C_{1-3}alkyl; n'' is 0 or 1 and X_5 is -NCS, -NCO, or a carboxy group or a functional derivative thereof.

4. A ligand according to any one of claim 1, 2 or 3 wherein the growth factor is EGF, IGF, fibroblast growth factor, tumor necrosis factor, transforming growth factor, platelet derived growth factor, nerve growth factor, LHRH, or bombesin or an analogue or derivative thereof or an LHRH agonist, LHRH antagonist.

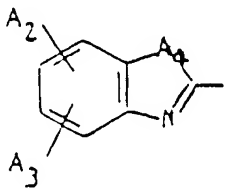
5. A ligand according to any one of the preceding claims wherein the peptide is a LHRH antagonist of formula VII

R_{33} - A_1 - B_1 - C_1 - D_1 - E_1 - F_1 - G_1 - H_1 - I_1 - K_1 - NH_2 (VII)

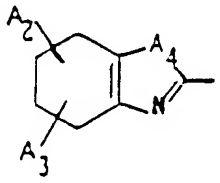
wherein

R_{33} is hydrogen, C_{1-7}acyl or carbamoyl,

A_1 is D-Phe optionally substituted in the phenyl ring by halogen, CF_3, C_{1-3}alkyl and/or C_{1-3}alkoxy, α- or β-naphthyl-D-alanine, D-Trp optionally substituted in 5 or 6 position by halogen or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, D- or L- Pro, D- or L-3,4-dehydroproline, D- or L-Ser, D- or L-Thr, D- or L-Ala, D-pyroglutamine, 3-(9-anthryl)-D,L-alanyl, 3-(2-fluorenyl)-D,L-alanyl or 3-(Het)-D,L-alanyl wherein Het is a heterocyclic aryl radical selected from



or



wherein

A_2 and A_3 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl, chlorine and bromine, and

A_4 is O, S or N

B_1 is D-Phe optionally substituted in the phenyl ring by halogen, NO_2, C_{1-3}alkyl or C_{1-3}alkoxy, D-α-methylPhe optionally substituted in 4 position by chlorine, 2,2-diphenylglycine or 3-(2-naphthyl)-D-alanine,

C_1 is D-Trp optionally substituted in 5 or 6 position by halogen, NO_2 or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, 3-(2- or 1-(naphthyl)-D-alanine, 3-D-pyridylalanine, D-Tyr, D-Phe optionally substituted by halogen, C_{1-3}alkyl and/or C_{1-3}alkoxy, D-3-Pz-Ala, D-Tin-Glu or D-Nic-Lys,

D_1 is L-Ser,

E_1 is Tyr, Phe optionally substituted in the phenyl ring by halogen, C_{1-3}alkyl and/or C_{1-3}alkoxy, Orn, Lys, Lys-Nic, MPic-Lys, Pic-Lys, DPic-Lys, Mpic-Lys, DMG-Lys, Pmc-Lys, Pzc-Lys, PmACAla, PzACAla, His, Dpo, Arg, 3-(3-pyridyl)-Ala, Trp, N-(3-pyridyl)acetyl-Lys or Glu(pMeO-phenyl), Cit, HOBLys or PzACAla,

F_1 is D-Phe optionally substituted in the phenyl ring by halogen, NO_2, NH_2, C_{1-3}alkyl or C_{1-3}alkoxy, D-Trp optionally substituted in 5 or 6 position by halogen, NO_2 and/or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, 3-(2-naphthyl)-L-alanyl, D-Tyr, D-Orn, D-Lys, D-Lys-Nic, D-MNic-Lys, D-MPic-Lys, Pic-Lys, DPic-Lys, D-Pmc-Lys, D-Pzc-Lys, D-Bz-Lys, D-lLys, AnGlu, D-NACAla, D-PzACAla, D-PmACAla, D-3-(3-pyridyl)-Ala, D-His (subst. H or benzyl), D-Arg, D-homo-Arg(Et_2), D-Cit, D-HCi, D-Lys-Pic, D-Cit(C_{1-3}alkyl), D-HCi-(C_{1-3}alkyl), D-Glu(AA) or α-amino-ω-ureido-C_{2-4}alkanoic acid,

G_1 is Leu, Nle, Nval, N-α-methylLeu, Trp, Phe, Met, Tyr, Val, Ile, alloIle, Abu or Ala,

H_1 is Arg, lOrn, Lys, lLys or Cyp-Lys

I_1 is Pro, hydroxyproline, 3,4-dehydroproline, Pip and

K_1 is D-Ala, D-Leu, Gly, D-Ser or Sar, in free form or in salt form.

6. A ligand according to any one of the preceding claims wherein the peptide is a bombesin antagonist of formula IXa

$$R_{36} - A_6 - B_3 - C_3 - D_3 - E_3 - F_3 - G_3 - H_3 - I_3 - Q \quad (IXa)$$
$$1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \quad 10$$

wherein

R_{36} is hydrogen, C_{1-6}alkyl, C_{2-6}alkanoyl, C_{4-6}cycloalkoxycarbonyl or C_{1-4}alkoxycarbonyl,
A_6 is a direct bond or Gly, Arg, Lys, Phe, Asp, Nal, Pro, β-Ala or Glp,
B_3 is a direct bond or Gly, Pro or Asn,
C_3 is a direct bond or Lys or D-Nal,
D_3 is a direct bond or His, MeHis, EtHis, PrHis, Gln, Glu (OMe)-Glp, Leu, MeLeu, Lys, Pal, Phe, Pro, Arg, Trp or Thr,
E_3 is Trp, Val, Nal, Leu, Lys, Pal,
F_3 is Ala, MeAla, Aib, Gly, Pro, Leu, Phe, Ser, Val, Nal, Thr, Arg or Glu,
G_3 is Val, Aib, Leu, Ile, Thr, Phe or Ser,
H_3 is Gly, Sar, Ala, Ser, Aib, Pro, Lys, Asp, Arg, Val, Ac^3c, Ac^5c or Ac^6c,
I_3 is His, MeHis, Aib, Val, Leu, MeLeu, Ala, Ile, Met, Pro, Phe, Gln, Lys, Pal, Ser, Thr, Glu, Asp, Trp or Nal, and
Q is K_3-R_{37} wherein K_3 is Leu, MeLeu, Ile, MeIle, Aib, Pro, Val, MeVal, Phe, Ape, MeApe, Met, Ser, Gln, Glu or Trp and R_{37} is C_{1-3}alkylamino, C_{1-4}(dialkyl)amino or C_{1-3}alkoxy or Q is C_{1-6}alkoxy, C_{1-10}alkylamino or C_{1-10}(dialkyl)amino,

or a compound of formula IXb

$$\underset{1}{A_7} - \underset{2}{B_4} - \underset{3}{Gln} - \underset{4}{Trp} - \underset{5}{Ala} - \underset{6}{Val} - \underset{7}{W} - \underset{8}{X_6} - \underset{9}{Y_6} - \underset{10}{T_1} \qquad (IXb)$$

wherein

A_7 is hydrogen, Boc, Lys, Arg,
B_4 is a direct bond or Asn, Thr, Glp,
W is Gly or Ala,
X_6 is a direct bond, His(R_{38}), Phe, Ser or Ala,
Y_6 is a direct bond, Leu or Phe,
T_1 is amino, $NH(CH_2)_4CH_3$, benzylamino, Met-R_{39}, Leu-R_{39}, Ile-R_{39}, Ile-R_{39} or Nle-R_{39},
R_{38} is hydrogen or benzyl, and
R_{39} is amino, hydroxy, methoxy or $-NHNH_2$,

in free form or in salt form.

7. A ligand according to any one of the preceding claims wherein the chelating group is attached to the terminal amino group.

8. A ligand according to any one of the preceding claims wherein the chelating group is attached to a side chain amino group.

9. A ligand which is

DTPA-β-Ala-mEGF, [DTPA-β-Ala-Trp^{14}]-tetragastrin, acetyl-DPhe(pCl)-DPhe(pCl)-DTrp-Ser-Tyr-DLys(DTPA)-Leu-Arg-Pro-DAla-NH_2, DTPA-DNal-$(2)^1$-DPhe(p-Cl)-DTrp-Ser-Tyr-DLys(CH_2-CHOH-CH_2OH)-Leu-Lys(CH_2-CHOH-CH_2OH)-Pro-DAla-NH_2 and acetyl-His-Trp-Ala-Val-DAla-Lys(β-Ala-DTPA)-Leu-OEt.

10. A process for the preparation of a ligand according to claim 1 or 3, comprising
a) removing at least one protecting group which is present in a peptide bearing a chelating group, or

b) linking together by an amide bond two peptide fragments each of them containing at least one amino acid in protected or unprotected form and one of them containing the chelating group, wherein the amide bond is in such a way that the desired amino acid sequence is obtained, and then effecting optionally stage a) of the process, or

c) linking together a chelating agent and the desired peptide in protected or unprotected form in such a way that the chelating group is fixed on the desired amino group of the peptide, and then effecting optionally stage a), or

d) removing a functional group of an unprotected or a protected peptide bearing a chelating group or converting it into another functional group so that another unprotected or a protected peptide bearing a chelating group is obtained and in the latter case effecting stage a) of the process,

and recovering the ligand thus obtained in free form or in salt form.

11. A pharmaceutical composition comprising a ligand according to any one of claims 1 to 9, in free form or in pharmaceutically acceptable salt form in association with a pharmaceutically acceptable carrier or diluent.

12. A ligand as defined in any one of claims 1 to 9, complexed with a detectable element, in free form or in pharmaceutically acceptable salt form.

13. A ligand according to claim 12 wherein the detectable element is a fluorescent or a α-, β- or γ-emitting element.

14. A ligand according to claim 12, in free form or in pharmaceutically acceptable salt form, for use as a pharmaceutical.

15. A ligand according to claim 12, in free form, for use as an imaging agent when the detectable element is a fluorescent or γ-emitting element, or for use in therapy when the detectable element is an α- or β-emitting element.

16. A pharmaceutical composition comprising a ligand according to claim 12, in free form or in pharmaceutically acceptable salt form in association with a pharmaceutically acceptable carrier or diluent.

17. A process for the production of a ligand according to claim 12, comprising complexing a ligand, according to any one of claims 1 to 9, in free form or in salt form, with a detectable element yielding compound.

18. A compound of formula XII

$A\text{-}Z'_1\text{-}CO\text{-}X_7$ (XII)

wherein

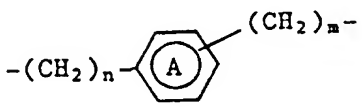
A is a polyamino polycarboxylic chelating group

Z'_1 is either a direct bond or -Z-R wherein Z is NH or CO and

R is C_{1-11}alkylene, hydroxy substituted C_{2-11}alkylene, C_{2-11}alkenylene,

$$-\underset{\displaystyle R_5}{\overset{\displaystyle |}{CH}}-,$$

cyclohexylene, substituted cyclohexylene, or a radical of formula (α_2)



(α_2)

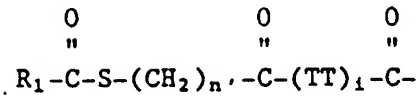
wherein each of n and m independently is 0, 1, 2 or 3, the ring A is substituted or unsubstituted, and

R_5 is a residue as attached in Cα of a natural or synthetic α-amino acid, and

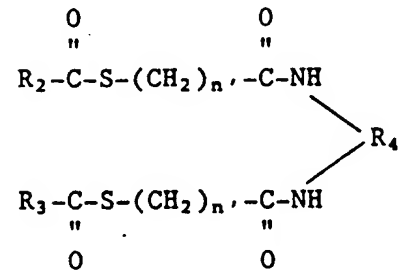
X_7 is -NH-NH_2 in protected or unprotected form or -N_3.

Claims for the following Contracting State : ES

1. A process for the production of a ligand comprising a biologically active peptide selected from the group consisting of growth factors, insulin, LHRH, gastrin, gastrin releasing peptide, thyrotropin releasing hormone, thyroid stimulating hormone, prolactin, vasoactive intestinal peptide, angiotensin, interferons, IL-1, IL-4 and IL-6, and analogues or derivatives thereof and bearing at least one chelating group selected from polyamino polycarboxylic groups, a group of formula IIa or IIb,



(IIa)

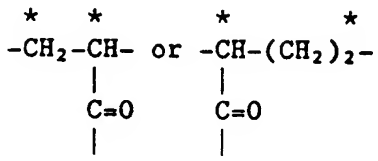


(IIb)

wherein

each of R_1, R_2 and R_3 independently is C_{1-6}alkyl, C_{6-8}aryl or C_{7-9}arylalkyl, each optionally substituted by OH, C_{1-4}alkoxy, COOH or SO_3H,

R_4 is



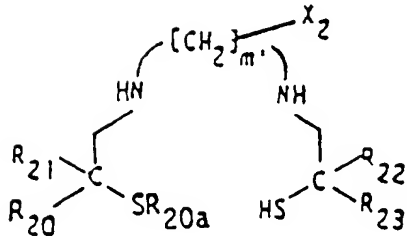
wherein the carbon atoms marked with * are attached to the imino groups,

n' is 1 or 2,

i is an integer from 2 to 6, and

TT are independently α or β amino acids linked to each other by amide bonds,

or a group derived from compounds of formula III



(III)

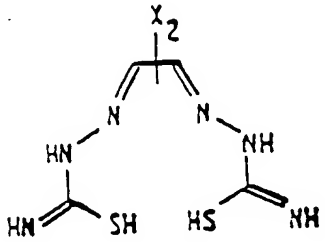
wherein

each of R_{20}, R_{20a}, R_{21}, R_{22} and R_{23} independently is hydrogen or C_{1-4} alkyl,

X_2 is either a group capable of reacting with the N-amino group of the peptide, or a group capable of binding with the divalent bridging group and

m' is 2 or 3,

from compounds of formula IV

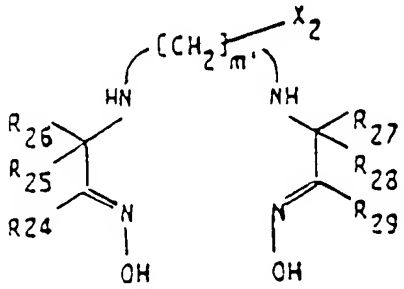


(IV)

wherein

X_2 is as defined above,

from compounds of formula V

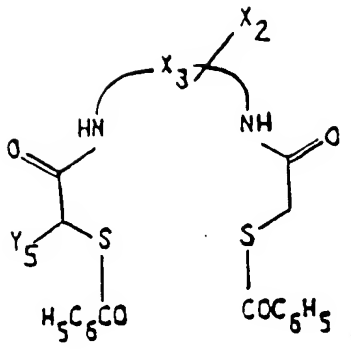


(V)

wherein

each of R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and R_{29} independently is hydrogen or C_{1-4} alkyl, and

X_2 and m' are as defined above, from compounds of formula VI



(VI)

wherein

X_2 is as defined above,

X_3 is C_{1-4}alkylene, C_{1-4}alkylene substituted by one or two CO_2R_{30}, by CH_2COR_{30}, $CONH_2$ or $CONHCH_2CO_2R_{30}$, phenylene, or phenylene substituted by CO_2R_{30} wherein R_{30} is C_{1-4}alkyl, and

Y_5 is hydrogen or CO_2R_{30},

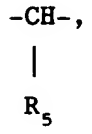
from porphyrins or from Desferal,

the chelating group being linked either directly or indirectly by means of a divalent bridging group to an amino group of said peptide in such a way to form an amide bond, the divalent bridging group being a group of formula α_1

Z-R-CO- (α_1)

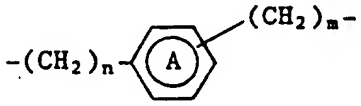
wherein

R is C_{1-11}alkylene, hydroxy substituted C_{2-11}alkylene, C_{2-11}alkenylene,



cyclohexylene, substituted cyclohexylene,

or a radical of formula (α_2)



(α_2)

wherein n and m are as defined above,

the ring A is substituted or unsubstituted, and

R_5 is a residue as attached in Cα of a natural or synthetic α-amino acid, and

Z is NH or CO, said amino group of the peptide being not directly attached to an aromatic residue, the chelating group being capable of complexing a detectable element and the amino group of said peptide having no significant binding affinity to target receptors, with the proviso that the chelating group is other than EDTA or substituted EDTA when the peptide is insulin,

in free form or in salt form,

which process comprises

a) removing at least one protecting group which is present in a peptide bearing a chelating group, or

b) linking together by an amide bond two peptide fragments each of them containing at least one amino acid in protected or unprotected form and one of them containing the chelating group,

wherein the amide bond is in such a way that the desired amino acid sequence is obtained, and then effecting optionally stage a) of the process, or

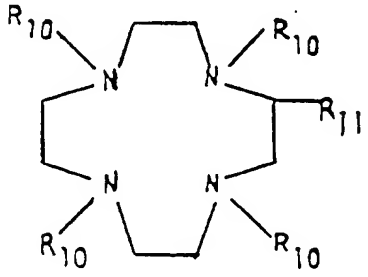
c) linking together a chelating agent and the desired peptide in protected or unprotected form in such a way that the chelating group is fixed on the desired amino group of the peptide, and then effecting optionally stage a), or

d) removing a functional group of an unprotected or a protected peptide bearing a chelating group or converting it into another functional group so that another unprotected or a protected peptide bearing a chelating group is obtained and in the latter case effecting stage a) of the process,

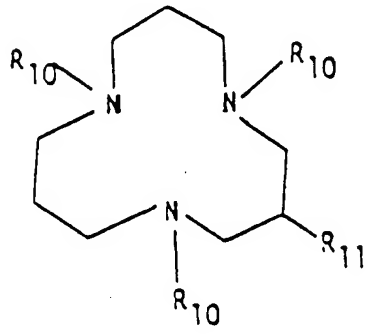
and recovering the ligand thus obtained in free form or in salt form.

2. A process according to claim 1 for the production of a ligand wherein the chelating group is a polyamino poly(acetic acid) group selected from a group derived from diethylene triamine pentaacetic acid (DTPA), N-hydroxyethyl-N,N',N'-ethylene diaminetriacetic acid (HEDTA), ethylene glycol-O,O'-bis-(2-aminoethyl)-N,N,N',N'-tetraacetic acid (EGTA), N,N'-bis(hydroxybenzyl)-ethylenediamine-N,N'-diacetic acid (HBED), triethylenetetramine hexaacetic acid (TTHA), from substituted EDTA or -DTPA, from 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA), 1,4,8,11-tetraazacyclotetradecane-N,N',N'',N'''-tetraacetic acid (TETA), the chelating group being other than substituted EDTA when the peptide is insulin.

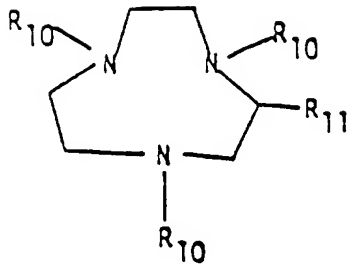
3. A process according to claim 1 for the production of a ligand comprising a biologically active peptide selected from the group consisting of growth factors, insulin, LHRH, gastrin, gastrin releasing peptide, thyrotropin releasing hormone, thyroid stimulating hormone, prolactin, vasoactive intestinal peptide, angiotensin, interferons, IL-1, IL-4 and IL-6, and analogues or derivatives thereof and bearing at least one chelating group derived from N'-p-isothiocyanato-benzyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N'-p-isothiocyanatophenethyl-diethylene triamine-N,N,N'',N''-tetraacetic acid, N-{2-[bis-(carboxymethyl)amino]ethyl}-N'-{2-[bis(carboxymethyl)amino]-2-(p-isothiocyanatobenzyl)ethyl}-glycine, a compound of formula Ia, Ib or Ic,



(Ia)



(Ib)

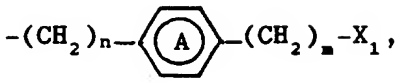


(Ic)

wherein

R_{10} is $-CH_2COOH$ or a functional derivative thereof, and

R_{11} is -Alk-X_1 or



wherein each of n and m independently is 0, 1, 2 or 3, Alk is C_{1-11}alkylene, X_1 is -NCS or NH_2 optionally substituted by a protecting group and ring A is substituted or unsubstituted, or a compound of formulae III to VI as defined in claim 1 wherein X_2 is $-(X_4)_{n''}-X_5$ wherein X_4 is C_{1-6}alkylene; C_{1-6}alkylene optionally attached to the carbon atom by an oxygen atom or -NH- or phenyl-C_{1-3}alkyl; n'' is 0 or 1 and X_5 is -NCS, -NCO, or a carboxy group or a functional derivative thereof.

4. A process according to claim 1 for the production of a ligand wherein the growth factor is EGF, IGF, fibroblast growth factor, tumor necrosis factor, transforming growth factor, platelet derived growth factor, nerve growth factor, LHRH, or bombesin or an analogue or derivative thereof or an LHRH agonist, LHRH antagonist.

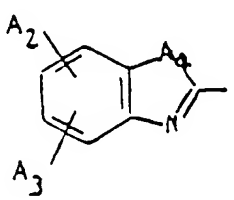
5. A process according to claim 1 for the production of a ligand wherein the peptide is a LHRH antagonist of formula VII

R_{33} - A_1 - B_1 - C_1 - D_1 - E_1 - F_1 - G_1 - H_1 - I_1 - K_1 - NH_2 (VII)

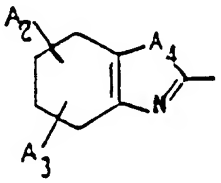
wherein

R_{33} is hydrogen, C_{1-7}acyl or carbamoyl,

A_1 is D-Phe optionally substituted in the phenyl ring by halogen, CF_3, C_{1-3}alkyl and/or C_{1-3}alkoxy, α- or β-naphthyl-D-alanine, D-Trp optionally substituted in 5 or 6 position by halogen or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, D- or L- Pro, D- or L-3,4-dehydroproline, D- or L-Ser, D- or L-Thr, D- or L-Ala, D-pyroglutamine, 3-(9-anthryl)-D,L-alanyl, 3-(2-fluorenyl)-D,L-alanyl or 3-(Het)-D,L-alanyl wherein Het is a heterocyclic aryl radical selected from



or



wherein

A_2 and A_3 are independently selected from the group consisting of hydrogen, C_{1-4}alkyl,

chlorine and bromine, and A_4 is O, S or N

B_1 is D-Phe optionally substituted in the phenyl ring by halogen, NO_2, C_{1-3} alkyl or C_{1-3} alkoxy, D-α-methylPhe optionally substituted in 4 position by chlorine, 2,2-diphenylglycine or 3-(2-naphthyl)-D-alanine,

C_1 is D-Trp optionally substituted in 5 or 6 position by halogen, NO_2 or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, 3-(2- or 1-(naphthyl)-D-alanine, 3-D-pyridylalanine, D-Tyr, D-Phe optionally substituted by halogen, C_{1-3}alkyl and/or C_{1-3} alkoxy, D-3-Pz-Ala, D-Tin-Glu or D-Nic-Lys,

D_1 is L-Ser,

E_1 is Tyr, Phe optionally substituted in the phenyl ring by halogen, C_{1-3}alkyl and/or C_{1-3}alkoxy, Orn, Lys, Lys-Nic, MPic-Lys, Lys-Pic, Mpic-Lys, DMG-Lys, Pmc-Lys, Pzc-Lys, His, Dpo, Arg, 3-(3-pyridyl)-Ala, Trp, N-(3-pyridyl)acetyl-Lys or Glu(pMeo-phenyl), Cit, HOBLys or PzACAla,

F_1 is D-Phe optionally substituted in the phenyl ring by halogen, NO_2, C_{1-3}alkyl or C_{1-3}alkoxy, D-Trp optionally substituted in 5 or 6 position by halogen, NO_2 and/or C_{1-3}alkoxy and/or in 1 position by formyl or acetyl, 3-(2-naphthyl)-L-alanyl, D-Tyr, D-Orn, D-Lys, D-Lys-Nic, D-MNic-Lys, D-MPic-Lys, D-Pmc-Lys, D-Pzc-Lys, D-Bz-Lys, D-ILys, AnGlu, D-NACAla, D-PzACAla, D-PmACAla, D-3-(3-pyridyl)-Ala, D-His (subst. H or benzyl), D-Arg, D-homo-Arg-(Et_2), D-Cit, D-HCi, D-Lys-Pic, D-Cit(C_{1-3}alkyl), D-HCi(C_{1-3}alkyl), D-Glu(AA) or α-amino-ω ureido-C_{2-4}alkanoic acid,

G_1 is Leu, Nle, Nval, N-α-methylLeu, Trp, Phe, Met, Tyr, Val, Ile, alloIle, Abu or Ala,

H_1 is Arg, IOrn, ILys or Cyp-Lys

I_1 is Pro, hydroxyproline, 3,4-dehydroproline, Pip and

K_1 is D-Ala, D-Leu, Gly, D-Ser or Sar, in free form or in salt form.

6. A process according to claim 1 for the preparation of a ligand wherein the peptide is a bombesin antagonist of formula IXa

$$\underset{}{R_{36}} - \underset{1}{A_6} - \underset{2}{B_3} - \underset{3}{C_3} - \underset{4}{D_3} - \underset{5}{E_3} - \underset{6}{F_3} - \underset{7}{G_3} - \underset{8}{H_3} - \underset{9}{I_3} - \underset{10}{Q} \quad \text{(IXa)}$$

wherein

R_{36} is hydrogen, C_{1-6}alkyl, C_{2-6}alkanoyl, C_{4-6}cycloalkoxycarbonyl or C_{1-4}alkoxycarbonyl,

A_6 is a direct bond or Gly, Arg, Lys, Phe, Asp, Nal, Pro, β-Ala or Glp,

B_3 is a direct bond or Gly, Pro or Asn,

C_3 is a direct bond or Lys or D-Nal,

D_3 is a direct bond or His, MeHis, EtHis, PrHis, Gln, Glu (OMe)-Glp, Leu, MeLeu, Lys, Pal, Phe, Pro, Arg, Trp or Thr,

E_3 is Trp, Val, Nal, Leu, Lys, Pal,

F_3 is Ala, MeAla, Aib, Gly, Pro, Leu, Phe, Ser, Val, Nal, Thr, Arg or Glu,

G_3 is Val, Aib, Leu, Ile, Thr, Phe or Ser,

H_3 is Gly, Sar, Ala, Ser, Aib, Pro, Lys, Asp, Arg, Val, Ac^3c, Ac^5c or Ac^6c,

I_3 is His, MeHis, Aib, Val, Leu, MeLeu, Ala, Ile, Met, Pro, Phe, Gln, Lys, Pal, Ser, Thr, Glu, Asp, Trp or Nal, and

Q is K_3-R_{37} wherein K_3 is Leu, MeLeu, Ile, MeIle, Aib, Pro, Val, MeVal, Phe, Ape, MeApe, Met, Ser, Gln, Glu or Trp and R_{37} is C_{1-3}alkylamino, C_{1-4}(dialkyl)amino or C_{1-3}alkoxy or Q is C_{1-6}alkoxy, C_{1-10}alkylamino or C_{1-10}(dialkyl)amino,

or a compound of formula IXb

$$\underset{1}{A_7} - \underset{2}{B_4} - \underset{3}{Gln} - \underset{4}{Trp} - \underset{5}{Ala} - \underset{6}{Val} - \underset{7}{W} - \underset{8}{X_6} - \underset{9}{Y_6} - \underset{10}{T_1} \quad \text{(IXb)}$$

wherein

A_7 is hydrogen, Boc, Lys, Arg,

B_4 is a direct bond or Asn, Thr, Glp,
W is Gly or Ala,
X_6 is a direct bond, His(R_{38}), Phe, Ser or Ala,
Y_6 is a direct bond, Leu or Phe,
T_1 is amino, $NH(CH_2)_4CH_3$, benzylamino, Met-R_{39}, Leu-R_{39}, Ile-R_{39}, Ile-R_{39} or Nle-R_{39},
R_{38} is hydrogen or benzyl, and
R_{39} is amino, hydroxy, methoxy or $-NHNH_2$,
in free form or in salt form.

7. A process according to claim 1 for the preparation of a ligand which is

DTPA-β-Ala-mEGF, [DTPA-β-Ala-Trp^{14}]-tetragastrin, acetyl-DPhe(pCl)-DPhe(pCl)-DTrp-Ser-Tyr-DLys(DTPA)-Leu-Arg-Pro-DAla-NH_2, DTPA-DNal-(2)^1-DPhe-(p-Cl)-DTrp-Ser-Tyr-DLys(CH_2-CHOH-CH_2OH)-Leu-Lys-CH_2-CHOH-CH_2OH)-Pro-DAla-NH_2 and acetyl-His-Trp-Ala-Val-DAla-Lys(β-Ala-DTPA)-Leu-OEt.

8. A process according to any one of the preceding claims which comprises the further step of complexing the ligand with a detectable element yielding compound.

9. A process according to claim 8 wherein the detectable element is a fluorescent or a α-, β or γ-emitting element.

10. A process according to any one of the preceding claims wherein the compound prepared is mixed with a pharmaceutically acceptable carrier or diluent.

11. The use of a ligand prepared according to claims 8 or 9 in the manufacture of an imaging agent when the detectable element is a fluorescent or γ-emitting element, or in the manufacture of a therapeutical agent when the detectable element is a α- or β-emitting element.

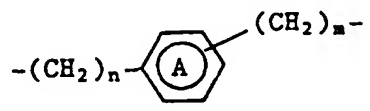
12. A process for the preparation of a compound of formula (XII)

$A\text{-}Z'_1\text{-}CO\text{-}X_7$ (XII)

wherein
A is a polyamino polycarboxylic chelating group
Z'_1 is either a direct bond or -Z-R wherein Z is NH or CO and
R is C_{1-11}alkylene, hydroxy substituted C_{2-11}alkylene, C_{2-11}alkenylene,

$$-\underset{\displaystyle R_5}{\overset{\displaystyle |}{CH}}-,$$

cyclohexylene, substituted cyclohexylene, or a radical of formula (α_2)



(α_2)

wherein each of n and m independently is 0, 1, 2 or 3, the ring A is substituted or unsubstituted, and

R_5 is a residue as attached in Cα of a natural or synthetic α-amino acid, and

X_7 is -NH-NH_2 in protected or unprotected form or -N_3,

comprising reacting a compound of formula XI

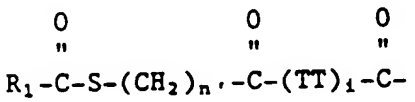
A - Z - R - Z_2 (XI)

wherein A and R are as defined above, Z is CO or NH and Z_2 is COOH, or a chelating agent bearing a reactive -COOH, or a functional derivative thereof, with hydrazine or a derivative thereof and then converting the resulting compound into an azide.

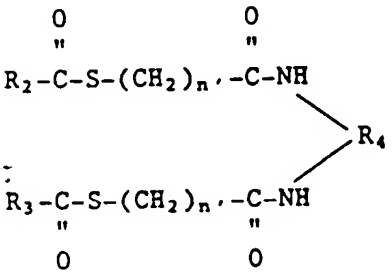
Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Ein Ligand bestehend aus einem biologisch-aktiven Peptid, wobei das Peptid ausgewählt ist aus der Gruppe von Wachstumsfaktoren, Insulin, LHRH, Gastrin, GRP, Thyroliberin, Thyreotropin, Prolactin, vasoaktivem intestinalem Peptid, Hypertensin, Interferonen, IL-1, IL-4 und IL-6, und Analogen oder Derivaten davon und wobei das Peptid mindestens eine chelatbildende Gruppe trägt, ausgewählt unter Polyamino Polycarboxygruppen, eine Gruppe der Formel IIa oder IIb



(IIa)



(IIb)

worin

R_1, R_2 und R_3 jeweils unabhängig voneinander C_{1-6}Alkyl, C_{6-8}Aryl oder C_{7-9}Arylalkyl bedeuten, die jeweils gegebenenfalls durch OH, C_{1-4}Alkoxy, COOH oder SO_3H substituiert sein können,

R_4

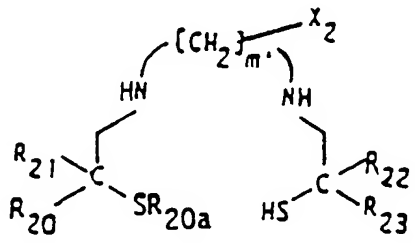
ist, worin die mit * bezeichneten Kohlenstoffatome an die Iminogruppen gebunden sind,

n' 1 oder 2 ist,

i eine ganze Zahl von 2 bis 6 ist, und

TT unabhängig voneinander α- oder β-Aminosäuren bedeuten, die miteinander durch Amidbindungen verknüpft sind,

eine Gruppe, die sich von Verbindungen der Formel III ableitet



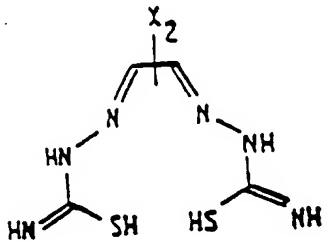
(III)

worin R_{20}, R_{20a}, R_{21}, R_{22} und R_{23} jeweils unabhängig voneinander Wasserstoff oder C_{1-4}Alkyl bedeuten,

X_2 eine Gruppe bedeutet, die entweder zur Reaktion mit der N-Aminogruppe des Peptids oder zur Verknüpfung mit der divalenten Brückengruppe in der Lage ist, und

m' 2 oder 3 ist,

eine Gruppe, die sich von Verbindungen der Formel IV ableitet

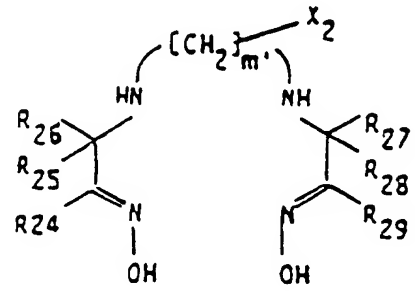


(IV)

worin

X_2 die vorstehend definierte Bedeutung hat,

eine Gruppe, die sich von Verbindungen der Formel V ableitet



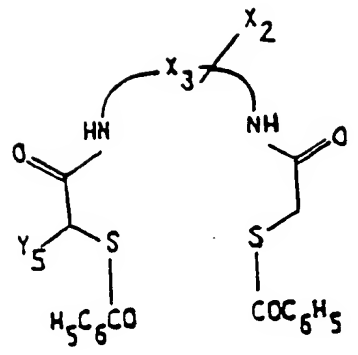
(V)

worin

R_{24}, R_{25}, R_{26}, R_{27}, R_{28} und R_{29} jeweils unabhängig voneinander Wasserstoff oder C_{1-4}Alkyl bedeuten, und

X_2 und m' wie oben definiert sind,

eine Gruppe, die sich von Verbindungen der Formel VI ableitet



(VI)

worin

X_2 wie oben definiert ist,

X_3 gegebenenfalls durch ein oder zwei CO_2R_{30} oder gegebenenfalls durch CH_2CO_{30}, $CONH_2$ oder $CONHCH_2CO_2R_{30}$ substituiertes C_{1-4}Alkylen, gegebenenfalls durch CO_2R_{30} substituiertes Phenylen ist, wobei R_{30} C_{1-4}Alkyl bedeutet, und

Y_5 Wasserstoff oder CO_2R_{30} bedeutet,

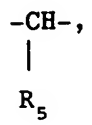
oder eine Gruppe, die sich von Porphyrinen oder Desferal ableitet, wobei die chelatbildende Gruppe entweder direkt oder

indirekt durch eine divalente Brückengruppe an die Aminogruppe des Peptids so verknüpft ist, dass eine Amidbindung gebildet ist, wobei die divalente Brückengruppe eine Gruppe der Formel α_1 ist

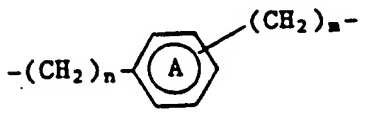
Z-R-CO- (α_1)

worin

R C_{1-11}Alkylen, Hydroxy-substituiertes C_{2-11}Alkylen, C_{2-11}Alkenylen,



Cyclohexylen, substituiertes Cyclohexylen,
oder ein Radikal der Formel (α_2) ist



(α_2)

worin n und m wie oben definiert sind, der Ring A substituiert oder unsubstituiert ist, und

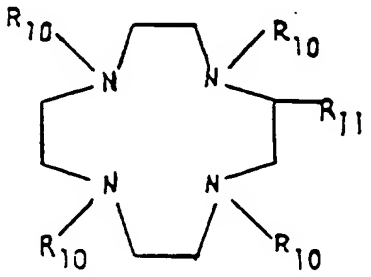
R_5 den in Cα einer natürlichen oder synthetischen α-Aminosäure-gebundenen Rest bedeutet, und

Z NH oder CO ist, wobei die Aminogruppe des Peptids nicht direkt an einen aromatischen Rest gebunden ist, wobei die chelatbildende Gruppe ein nachweisbares Element komplexieren kann und die Aminogruppe des Peptids keine signifikante Bindungsaktivität für die gezielten Rezeptoren aufweist, mit der Massgabe, dass die chelatbildende Gruppe verschieden von EDTA oder substituiertem EDTA ist, wenn das Peptid Insulin ist, in freier Form oder in Salzform.

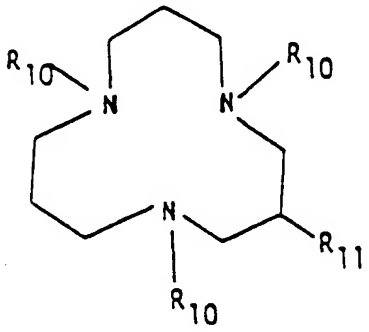
2. Ein Ligand nach Anspruch 1 worin die chelatbildende Gruppe eine Polyamino Polyessigsäuregruppe ist, die unter einer Gruppe abgeleitet von Diethylentriaminpentaessigsäure (DTPA), N-Hydroxyethyl-N,N',N'-Ethylendiamintriessigsäure (HEDTA), Ethylenglycol-O,O'-bis(2-Aminoethyl)-N,N,N',N'-tetraessig-

säure (EGTA), N,N'-bis(Hydroxybenzyl)-Ethylendiamin-N,N'-Diessigsäure (HBED), Triethylentetraminhexaessigsäure (TTHA), substituierter EDTA oder -DTPA, 1,4,7,10-Tetraazacyclododecan-N,N',N'',N'''-Tetraessigsäure (DOTA), 1,4,8,11-Tetraazacyclotetradecan-N,N',N'',N'''-Tetraessigsäure (TETA) ausgewählt ist, wobei die chelatbildende Gruppe verschieden von substituierter EDTA ist, wenn das Peptid Insulin ist.

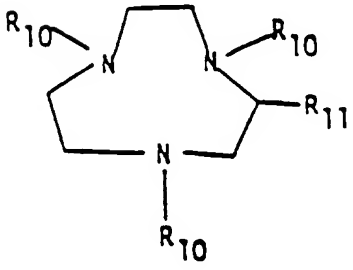
3. Ein Ligand bestehend aus einem biologisch aktiven Peptid, wobei das Peptid ausgewählt ist aus der Gruppe von Wachstumsfaktoren, Insulin, LHRH, Gastrin, GRP, Thyroliberin, Thyreotropin, Prolactin, vasoaktivem intestinalem Peptid, Hypertensin, Interferonen, IL-1, IL-4 und IL-6, und Analogen oder Derivaten davon und wobei das Peptid mindestens eine chelatbildende Gruppe, die von N'-p-Isothiocyanatobenzyl-diethylentriamin-N,N,N'',N''-tetra essigsäure, N'-p-isothiocyanatophenethyl-diethylentriamin-N,N,N'',N'',-Tetraessigsäure, N-{2-[Bis(carboxymethyl)-amino]ethyl}-N'-{2-[bis(carboxymethyl)-amino]-2-(p-isothiocyanatobenzyl)-ethyl}-glycin, einer Verbindung der Formel Ia, Ib oder Ic



(Ia)



(Ib)

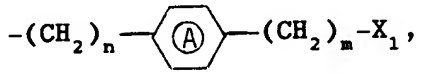


(Ic)

worin

R_{10} $-CR_2COOH$ oder ein funktioneller Derivat davon ist, und

R_{11} -Alk-X_1 oder



worin n und m jeweils unabhängig voneinander 0, 1, 2 oder 3 bedeuten, Alk C_{1-11}Alkylen ist, X_1 -NCS oder gegebenenfalls durch eine Schutzgruppe substituiertes NE_2 ist und der Ring A substituiert oder unsubstituiert ist,

oder von einer Verbindung der Formel III bis VI wie im Anspruch 1 definiert, worin X_2 einen Rest $-(X_4)_{n''}-X_5$ bedeutet, wobei X_4 C_{1-6}Alkylen gegebenenfalls durch ein Sauerstoffatom oder -NH- an das Kohlenstoffatom verknüpft ist, oder Phenyl-C_{1-3}Alkyl bedeutet; n'' 0 oder 1 ist, und X_5 -NCS, -NCO oder eine Carboxygruppe oder einen funktionellen Derivat davon bedeutet, abgeleitet ist.

4. Ein Ligand nach einem der Ansprüche 1, 2 oder 3 worin der Wachstumsfaktor EGF, IGF, Fibroplasten-Wachstumsfaktor, Tumornekrose-Faktor, TGF, PDGF, Nervenwachstumsfaktor, LHRH, oder Bombesin oder ein Analog oder Derivat davon oder ein LHRH-Agonist oder LHRH-Antagonist ist.

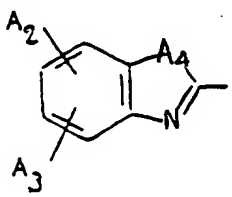
5. Ein Ligand nach einem der vorstehenden Ansprüche, wobei das Peptid ein LHRH Antagonist der Formel VII ist

$$R_{33} - A_1 - B_1 - C_1 - D_1 - E_1 - F_1 - G_1 - H_1 - I_1 - K_1 - NH_2 \qquad (VII)$$

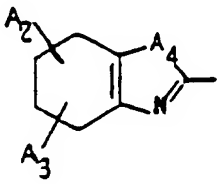
worin

R_{33} Wasserstoff, C_{1-7}Acyl or Carbamoyl ist,

A_1 D-Phe, wobei der Phenylring gegebenenfalls durch Halogen, CF_3, C_{1-3}Alkyl und/oder C_{1-3}Alkoxy substituiert ist, α- or β-Naphthyl-D-alanin, gegebenenfalls in Stellung 5 oder 6 durch Halogen oder C_{1-3}Alkoxy und/oder in Stellung 1 durch Formyl oder Acetyl substituiertes D-Trp, D- oder L- Pro, D- oder L-3,4-Dehydroprolin, D- oder L-Ser, D- oder L-Thr, D- oder L-Ala, D-Pyroglutamin, 3-(9-Anthryl)D-,L-alanyl, 3-(2-Fluorenyl)-D,L-alanyl oder 3-(Het)-D,L-alanyl ist, wobei Het einen heterozyklischen Arylrest ausgewählt unter



oder



ist, worin

A_2 und A_3 unabhängig voneinander unter der Gruppe von Wasserstoff, C_{1-4}Alkyl, Chlor und Brom, ausgewählt sind, und A_4 O, S oder N ist,

B_1 D-Phe, wobei der Phenylring gegebenenfalls durch Halogen, NO_2, C_{1-3}Alkyl oder C_{1-3}Alkoxy substituiert ist, gegebenenfalls in Stellung 4 durch Chlor substituiertes D-α-MethylPhe, oder 2,2-Diphenylglycin oder 3-(2-Naphthyl)-D-alanin ist,

C_1 gegebenenfalls in Stellung 5 oder 6 durch Halogen, NO_2 oder C_{1-3}Alkoxy und/oder in Stellung 1 durch Formyl oder Acetyl substituiertes D-Trp, 3-(2- or 1-(Naphthyl)-D-Alanin, 3-D-Pyridylalanin, D-Tyr, gegebenenfalls durch Halogen, C_{1-3}Alkyl und/oder C_{1-3}Alkoxy substituiertes DPhe, oder D-3-Pz-Ala, D-Tin-Glu oder D-Nic-Lys ist,

D_1 is L-Ser bedeutet,

E_1 Tyr, Phe, wobei der Phenylring gegebenenfalls durch Halogen, C_{1-3}Alkyl und/oder C_{1-3}Alkoxy substituiert ist, Orn, Lys, Lys-Nic, MPic-Lys, Pic-Lys, Dpic-Lys, MPic-Lys, DMG-Lys, Pmc-Lys, Pzc-Lys, PmACAla, His, Dpo, Arg, 3-(3-Pyridyl)-Ala, Trp, N-(3-Pyridyl)-acetyl-Lys oder Glu(pMeO-phenyl), Cit, HOBLys oder PzACAla bedeutet,

F_1 D-Phe, wobei der Phenylring gegebenenfalls durch Halogen, NO_2, C_{1-3}Alkyl oder C_{1-3}Alkoxy substituiert ist, gegebenenfalls in Stellung 5 oder 6 durch Halogen, NO_2 und/oder C_{1-3}Alkoxy und/oder in Stellung 1 durch Formyl oder Acetyl substituiertes D-Trp, 3-(2-Naphthyl)-L-alanyl, D-Tyr, D-Orn, D-Lys, D-Lys-Nic, D-MNic-Lys, D-MPic-Lys, Pic-Lys, DPic-Lys, D-Pmc-Lys, D-Pzc-Lys, D-Bz-Lys, D-ILys, AnGlu, D-NACAla, D-PzACAla, D-PmACAla, D-3-(3-Pyridyl)-Ala, D-His (H oder Benzyl subst.), D-Arg, D-homo-Arg(Et_2), D-Cit, D-HCit, D-Lys-Pic, D-Cit(C_{1-3}Alkyl), D-HCit(C_{1-3}alkyl), D-Glu-

(AA) oder α-Amino-ω-ureido-C_{2-4}alkancarboxysäure ist,

G_1 Leu, NLe, Nval, N-α-MethylLeu, Trp, Phe, Met, Tyr, Val, Ile, alloIle, Abu oder Ala bedeutet,

H_1 Arg, IOrn, Lys, ILys oder Cyp-Lys bedeutet

I_1 Pro, Hydroxyprolin, 3,4-Dehydroprolin, Pip ist und

K_1 D-Ala, D-Leu, Gly, D-Ser oder Sar bedeutet,

in freier Form oder in Salzform.

6. Ein Ligand nach einem der nachstehenden Ansprüche, wobei das Peptid ein Bombesin-Antagonist der Formel IXa

$$\underset{}{R_{36}} - \underset{1}{A_6} - \underset{2}{B_3} - \underset{3}{C_3} - \underset{4}{D_3} - \underset{5}{E_3} - \underset{6}{F_3} - \underset{7}{G_3} - \underset{8}{H_3} - \underset{9}{I_3} - \underset{10}{Q} \quad \text{(IXa)}$$

worin

R_{36} Wasserstoff, C_{1-6}Alkyl, C_{2-6}Alkanoyl, C_{4-6}Cycloalkoxycarbonyl oder C_{1-4}Alkoxycarbonyl bedeutet,

A_6 eine direkte Bindung oder Gly, Arg, Lys, Phe, Asp, Nal, Pro, β-Ala oder Glp ist,

B_3 eine direkte Bindung oder Gly, Pro oder Asn ist,

C_3 eine direkte Bindung oder Lys oder D-Nal bedeutet,

D_3 eine direkte Bindung oder His, MeHis, EtHis, PrHis, Gln, Glu (OMe)-Glp, Leu, MeLeu, Lys, Pal, Phe, Pro, Arg, Trp oder Thr ist,

E_3 Trp, Val, Nal, Leu, Lys, Pal bedeutet,

F_3 Ala, MeAla, Aib, Gly, Pro, Leu, Phe, Ser, Val, Nal, Thr, Arg oder Glu ist,

G_3 Val, Aib, Leu, Ile, Thr, Phe oder Ser ist,

H_3 Gly, Sar, Ala, Ser, Aib, Pro, Lys, Asp, Arg, Val, Ac^3c, Ac^5c oder Ac^6c ist,

I_3 His, MeHis, Aib, Val, Leu, MeLeu, Ala, Ile, Met, Pro, Phe, Gln, Lys, Pal, Ser, Thr, Glu, Asp, Trp oder Nal bedeutet, und

Q K_3-R_{37} bedeutet, worin K_3 Leu, MeLeu, Ile, MeIle, Aib, Pro, Val, MeVal, Phe, Ape, MeApe, Met, Ser, Gln, Glu oder Trp und R_{37} is C_{1-3}Alkylamino, C_{1-4}(Dialkyl)amino or C_{1-3}Alkoxy ist oder Q C_{1-6}Alkoxy, C_{1-10}Alkylamino oder C_{1-10}(Dialkyl)amino ist,

oder eine Verbindung der Formel IXb ist

$$\underset{1}{A_7} - \underset{2}{B_4} - \underset{3}{Gln} - \underset{4}{Trp} - \underset{5}{Ala} - \underset{6}{Val} - \underset{7}{W} - \underset{8}{X_6} - \underset{9}{Y_6} - \underset{10}{T_1} \quad \text{(IXb)}$$

worin

A_7 Wasserstoff, Boc, Lys, Arg ist,

B_4 eine direkte Bindung oder Asn, Thr, Glp ist,

W Gly oder Ala bedeutet,

X_6 eine direkte Bindung, His(R_{38}), Phe, Ser oder Ala ist,

Y_6 eine direkte Bindung, Leu oder Phe ist,

T_1 Amino, $NH(CH_2)_4CH_3$, Benzylamino, Met-R_{39}, Leu-R_{39}, Ile-R_{39} oder Nle-R_{39} bedeutet,

R_{38} Wasserstoff oder Benzyl ist, und R_{39} Amino, Hydroxy, Methoxy oder -$NHNH_2$ bedeutet,

in freier Form oder in Salzform.

7. Ein Ligand nach einem der vorstehenden Ansprüche, wobei die chelatbildende Gruppe mit der terminalen Aminogruppe verknüpft ist.

8. Ein Ligand nach einem der vorstehenden Ansprüche, wobei die chelatbildende Gruppe mit einer Seitenkette-Aminogruppe verknüpft ist.

9. Ein Ligand, der

DTPA-β-Ala-mEGF, [DTPA-β-Ala-Trp^{14}]-tetragastrin, Acetyl-DPhe(pCl)-DPhe(pCl)-DTrp-Ser-Tyr-DLys(DTPA)-Leu-Arg-Pro-DAla-NH_2, DTPA-DNal-(2)^{1}-DPhe-(p-Cl)-DTrp-Ser-Tyr-DLys(CH_2-CHOH-CH_2OH)-Leu-Lys-CH_2-CHOH-CH_2OH)-Pro-DAla-NH_2 und Acetyl-His-Trp-Ala-Val-DAla-Lys(β-Ala-DTPA)-Leu-OEt ist.

10. Verfahren zur Herstellung eines Liganden nach Anspruch 1 oder 3, das durchgeführt wird
a) indem man mindestens eine Schutzgruppe, die in einem eine chelatbildende Gruppe tragenden Peptid enthalten ist, entfernt, oder
b) indem man zwei Peptidfragmente miteinander verknüpft, wobei jedes der Peptidfragmente mindestens eine Aminosäure in geschützter oder ungeschützter Form enthält und eines der beiden Fragmente die chelatbildende Gruppe enthält, wobei die Amidbindung in solcher Weise vorliegt, dass die gewünschte Aminosäuresequenz erhalten wird, und indem man gegebenenfalls anschliessend die Stufe a) durchführt, oder
c) indem man ein Chelator und das gewünschte Peptid in geschützter oder ungeschützter Form auf solche Weise miteinander verknüpft, dass die chelatbildende Gruppe an der gewünschten Aminogruppe des Peptids fixiert wird, und indem man anschliessend gegebenenfalls die Stufe a) durchführt, oder
d) indem man eine funktionelle Gruppe eines eine chelatbildende Gruppe tragenden ungeschützten oder geschützten Peptids entfernt oder in eine andere funktionelle Gruppe umwandelt, so dass ein anderes, eine chelatbildende Gruppe tragendes ungeschütztes oder geschütztes Peptid erhalten wird, und indem man im letztgenannten Fall die Stufe a) durchführt,
und indem man den auf diese Weise erhaltenen Liganden in freier Form oder in Salzform gewinnt.

11. Pharmazeutische Zusammensetzung, enthaltend einen Liganden nach einem der Ansprüche 1 bis 9, in freier Form oder in Form eines pharmazeutisch verträglichen Salzes zusammen mit einem pharmazeutisch verträglichen Trägerstoff oder Verdünnungsmittel.

12. Ein Ligand nach einem der Ansprüche 1 bis 9, wobei der Ligand mit einem nachweisbaren Element komplexiert ist, in freier Form oder in Form eines pharmazeutisch verträglichen Salzes.

13. Ein Ligand nach dem Anspruch 12, wobei es sich bei dem nachweisbaren Element um ein fluoreszierendes, α-, β- oder γ-emittierendes Element handelt.

14. Ein Ligand nach dem Anspruch 12, in freier Form oder in Form eines pharmazeutisch verträglichen Salzes, zur Verwendung als pharmazeutisches Mittel.

15. Ein Ligand nach dem Anspruch 12, in freier Form zur Verwendung als Abbildungsmittel wenn das nachweisbare Element ein fluoreszierendes oder γ-emittierendes Element ist, oder zur Verwendung in der Therapie wenn das nachweisbare Element ein α- oder β-emittierendes Element ist.

16. Pharmazeutische Zusammensetzung, enthaltend einen Liganden nach dem Anspruch 12, in freier Form oder in Form eines pharmazeutisch verträglichen Salzes zusammen mit einem pharmazeutisch verträglichen Trägerstoff oder Verdünnungsmittel.

17. Verfahren zur Herstellung eines Liganden nach dem Anspruch 12, wobei ein Ligand nach einem der Ansprüche 1 bis 9, in freier Form oder in Salzform, mit einer Verbindung, die ein nachweisbares Element ergibt, umsetzt.

18. Eine Verbindung der Formel XII

$A\text{-}Z'_1\text{-}CO\text{-}X_7$ (XII)

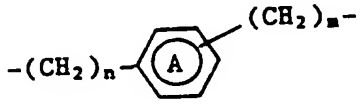
worin

A eine Polyaminopolyessigsäure chelatbildende Gruppe ist,

Z'_1 entweder eine direkte Bindung oder -Z-R-, worin Z NH oder CO ist, bedeutet, und

R C_{1-11} Alkylen, Hydroxy-substituiertes C_{2-11} Alkylen, C_{2-11} Alkenylen,

Cyclohexylen, substituiertes Cyclohexylen, oder ein Rest der Formel (α_2)



(α_2)

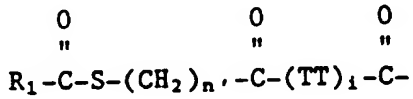
worin n und m unabhängig voneinander 0, 1, 2 or 3 bedeuten,
der Ring A substituiert oder unsubstituiert ist, und

R_5 den an $C\alpha$ gebundenen Rest einer natürlichen oder synthetischen Aminosäure bedeutet, und

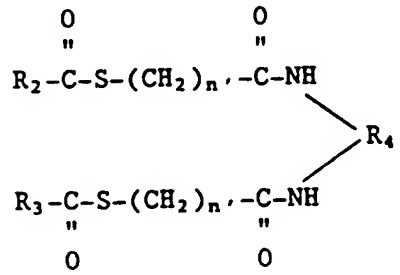
X_7 $-NH-NH_2$ in geschützter oder ungeschützter Form oder $-N_3$ bedeutet, ist.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung eines Liganden bestehend aus einem biologisch aktiven Peptid, wobei das Peptid ausgewählt ist aus der Gruppe von Wachstumsfaktoren, Insulin, LHRH, Gastrin, GRP, Thyroliberin, Thyreotropin, Prolactin, vasoaktivem intestinalem Peptid, Hypertensin, Interferonen, IL-1, IL-4 und IL-6, und Analogen oder Derivaten davon und wobei das Peptid mindestens eine chelatbildende Gruppe trägt, ausgewählt unter Polyamino Polycarboxygruppen, eine Gruppe der Formel IIa oder IIb



(IIa)

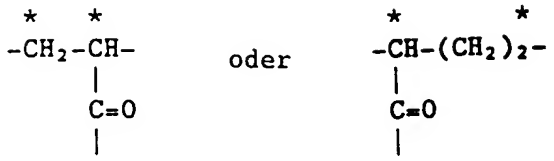


(IIb)

worin

R_1, R_2 und R_3 jeweils unabhängig voneinander C_{1-6} Alkyl, C_{6-8} Aryl oder C_{7-9} Arylalkyl bedeuten, die jeweils gegebenenfalls durch OH, C_{1-4} Alkoxy, COOH oder SO_3H substituiert sein können,

R_4



ist

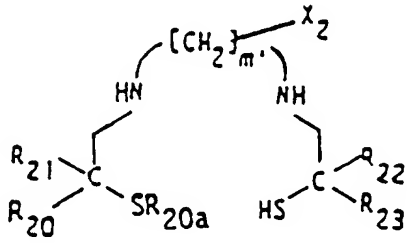
worin die mit * bezeichneten Kohlenstoffatome an die Iminogruppen gebunden sind,

n' 1 oder 2 ist,

i eine ganze Zahl von 2 bis 6 ist, und

TT unabhängig voneinander α- oder β-Aminosäuren bedeuten, die miteinander durch Amidbindungen verknüpft sind,

eine Gruppe, die sich von Verbindungen der Formel III ableitet



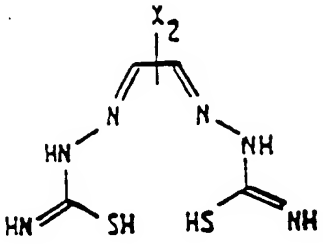
(III)

worin R_{20}, R_{20a}, R_{21}, R_{22} und R_{23} jeweils unabhängig voneinander Wasserstoff oder C_{1-4}Alkyl bedeuten,

X_2 eine Gruppe bedeutet, die entweder zur Reaktion mit der N-Aminogruppe des Peptids oder zur Verknüpfung mit der divalenten Brückengruppe in der Lage ist, und

m' 2 oder 3 ist,

eine Gruppe, die sich von Verbindungen der Formel IV ableitet

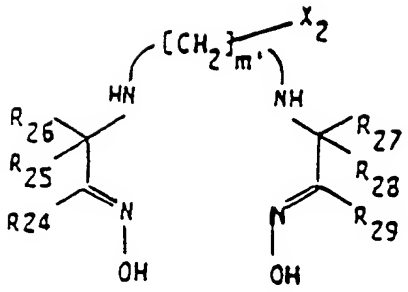


(IV)

worin

X_2 die vorstehend definierte Bedeutung hat,

eine Gruppe, die sich von Verbindungen der Formel V ableitet



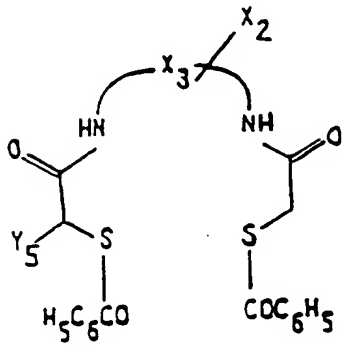
(V)

worin

R_{24}, R_{25}, R_{26}, R_{27}, R_{28} und R_{29} jeweils unabhängig voneinander Wasserstoff oder C_{1-4}Alkyl bedeuten, und

X_2 und m' wie oben definiert sind,

eine Gruppe, die sich von Verbindungen der Formel VI ableitet



(VI)

worin

X_2 wie oben definiert ist,

X_3 gegebenenfalls durch ein oder zwei CO_2R_{30} oder gegebenenfalls durch CH_2CO_{30}, $CONH_2$ oder $CONHCH_2CO_2R_{30}$ substituiertes C_{1-4}Alkylen, gegebenenfalls durch CO_2R_{30} substituiertes Phenylen ist, wobei R_{30} C_{1-4}Alkyl bedeutet, und

Y_5 Wasserstoff oder CO_2R_{30} bedeutet,

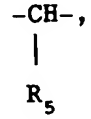
oder eine Gruppe, die sich von Porphyrinen oder Desferal ableitet,

wobei die chelatbildende Gruppe entweder direkt oder indirekt durch eine divalente Brückengruppe an die Aminogruppe des Peptids so verknüpft ist, dass eine Amidbindung gebildet ist, wobei die divalente Brückengruppe eine Gruppe der Formel α_1 ist

Z-R-CO- (α_1)

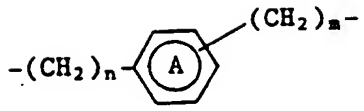
worin

R C_{1-11}Alkylen, Hydroxy-substituiertes C_{2-11}Alkylen, C_{2-11}Alkenylen,



Cyclohexylen, substituiertes Cyclohexylen,

oder ein Radikal der Formel (α_2) ist



(α_2)

worin n und m wie oben definiert sind, der Ring A substituiert oder unsubstituiert ist, und

R_5 den in Cα einer natürlichen oder synthetischen α-Aminosäure-gebundenen Rest bedeutet, und

Z NH oder CO ist, wobei die Aminogruppe des Peptids nicht direkt an einen aromatischen Rest gebunden ist, wobei die chelatbildende Gruppe ein nachweisbares Element komplexieren kann und die Aminogruppe des Peptids keine signifikante Bindungsaktivität für die gezielten Rezeptoren aufweist, mit der Massgabe, dass die chelatbildende Gruppe verschieden von EDTA oder substituiertem EDTA ist, wenn das Peptid Insulin ist, in freier Form oder in Salzform,

wobei das Verfahren durchgeführt wird

a) indem man mindestens eine Schutzgruppe, die in einem eine chelatbildende Gruppe tragenden Peptid enthalten ist, entfernt, oder

b) indem man zwei Peptidfragmente miteinander verknüpft, wobei jedes der Peptidfragmente mindestens eine Aminosäure in geschützter oder ungeschützter Form enthält und eines der beiden Fragmente die chelatbildende Gruppe enthält, wobei die Amidbindung in solcher Weise vorliegt, dass die gewünschte Aminosäuresequenz erhalten wird, und indem man gegebenenfalls anschliessend die Stufe a) durchführt, oder

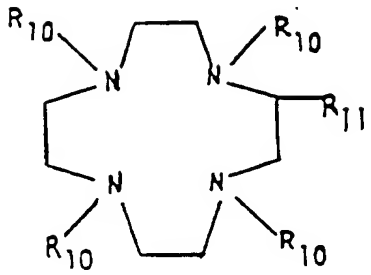
c) indem man ein Chelator und das gewünschte Peptid in geschützter oder ungeschützter Form auf solche Weise miteinander verknüpft, dass die chelatbildende Gruppe an der gewünschten Aminogruppe des Peptids fixiert wird, und indem man anschliessend gegebenenfalls die Stufe a) durchführt, oder

d) indem man eine funktionelle Gruppe eines eine chelatbildende Gruppe tragenden ungeschützten oder geschützten Peptids entfernt oder in eine andere funktionelle Gruppe umwandelt, so dass ein anderes, eine chelatbildende Gruppe tragendes ungeschütztes oder geschütztes Peptid erhalten wird, und indem man im letztgenannten Fall die Stufe a) durchführt,

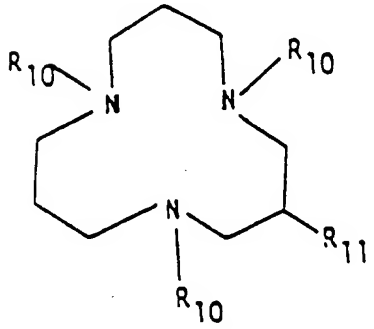
und indem man den auf diese Weise erhaltenen Liganden in freier Form oder in Salzform gewinnt.

2. Verfahren nach Anspruch 1 zur Herstellung eines Liganden worin die chelatbildende Gruppe eine Polyamino Polyessigsäuregruppe ist, die unter einer Gruppe abgeleitet von Diethylentriaminpentaessigsäure (DTPA), N-Hydroxyethyl-N,N',N'-Ethylendiamintriessigsäure (HEDTA), Ethylenglycol-O,O'-bis(2-Aminoethyl)-N,N,N',N'-tetraessigsäure (EGTA), N,N'-bis(Hydroxybenzyl)-Ethylendiamin-N,N'-Diessigsäure (HBED), Triethylentetraminhexaessigsäure (TTHA), substituierter EDTA oder -DTPA, 1,4,7,10-Tetraazacyclododecan-N,N',N'',N'''-Tetraessigsäure (DOTA), 1,4,8,11-Tetraazacyclotetradecan-N,N',N'',N'''-Tetraessigsäure (TETA) ausgewählt ist, wobei die chelatbildende Gruppe verschieden von substituierter EDTA ist, wenn das Peptid Insulin ist.

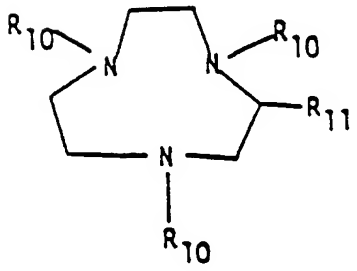
3. Verfahren nach Anspruch 1 zur Herstellung eines Liganden bestehend aus einem biologisch aktiven Peptid, wobei das Peptid ausgewählt ist aus der Gruppe von Wachstumsfaktoren, Insulin, LHRH, Gastrin, GRP, Thyroliberin, Thyreotropin, Prolactin, vasoaktivem intestinalem Peptid, Hypertensin, Interferonen, IL-1, IL-4 und IL-6, und Analogen oder Derivaten davon und wobei das Peptid mindestens eine chelatbildende Gruppe, die von N'-p-Isothiocyanatobenzyldiethylentriamin-N,N,N'',N''-tetraessigsäure, N'-p-isothiocyanatophenethyl-diethylentriamin-N,N,N'',N'',-Tetraessigsäure, N-{2-[Bis-(carboxymethyl)-amino]ethyl}-N'-{2-[bis-(carboxymethyl)amino]-2-(p-isothiocyanatobenzyl)ethyl}-glycin, einer Verbindung der Formel Ia, Ib oder Ic



(Ia)



(Ib)

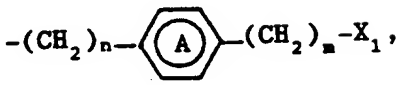


(Ic)

worin

R_{10} $-CH_2COOH$ oder ein funktioneller Derivat davon ist, und

R_{11} -Alk-X_1 oder



worin n und m jeweils unabhängig voneinander 0, 1, 2 oder 3 bedeuten, Alk C_{1-11}Alkylen ist, X_1 -NCS oder gegebenenfalls durch eine Schutzgruppe substituiertes NH_2 ist und der Ring A substituiert oder unsubstituiert ist,

oder von einer Verbindung der Formel III bis VI wie im Anspruch 1 definiert, worin X_2 einen Rest $-(X_4)-_{n''}-X_5$ bedeutet, wobei X_4 C_{1-6}Alkylen gegebenenfalls durch ein Sauerstoffatom oder -NH- an das Kohlenstoffatom verknüpft ist, oder Phenyl-C_{1-3}Alkyl bedeutet; n'' 0 oder 1 ist, und X_5 -NCS, -NCO oder eine Carboxygruppe oder einen funktionellen Derivat davon bedeutet, abgeleitet ist.

4. Verfahren nach Anspruch 1 zur Herstellung eines Liganden worin der Wachstumsfaktor EGF, IGF, Fibroplasten-Wachstumsfaktor, Tumornekrose-Faktor, TGF, PDGF, Nervenwachstumsfaktor, LHRH, oder Bombesin oder ein Analog oder Derivat davon oder ein LHRH-Agonist oder LHRH-Antagonist ist.

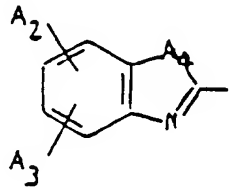
5. Verfahren nach Anspruch 1 zur Herstellung eines Liganden, wobei das Peptid ein LHRH Antagonist der Formel VII ist

R_{33} - A_1 - B_1 - C_1 - D_1 - E_1 - F_1 - G_1 - H_1 - I_1 - K_1 - NH_2 (VII)

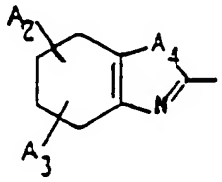
worin

R_{33} Wasserstoff, C_{1-7}Acyl or Carbamoyl ist,

A_1 D-Phe, wobei der Phenylring gegebenenfalls durch Halogen, CF_3, C_{1-3}Alkyl und/oder C_{1-3}Alkoxy substituiert ist, α- or β-Naphthyl-D-alanin, gegebenenfalls in Stellung 5 oder 6 durch Halogen oder C_{1-3}Alkoxy und/oder in Stellung 1 durch Formyl oder Acetyl substituiertes D-Trp, D- oder L- Pro, D- oder L-3,4-Dehydroprolin, D- oder L-Ser, D- oder L-Thr, D- oder L-Ala, D-Pyroglutamin, 3-(9-Anthryl)-D,L-alanyl, 3-(2-Fluorenyl)-D,L-alanyl oder 3-(Het)-D,L-alanyl ist, wobei Het einen heterozyklischen Arylrest ausgewählt unter



oder



ist, worin

A_2 und A_3 unabhängig voneinander unter der Gruppe von Wasserstoff, C_{1-4}Alkyl, Chlor und Brom, ausgewählt sind, und A_4 O, S oder N ist,

B_1 D-Phe, wobei der Phenylring gegebenenfalls durch Halogen, NO_2, C_{1-3}Alkyl oder C_{1-3}Alkoxy substituiert ist, gegebenenfalls in Stellung 4 durch Chlor substituiertes D-α-MethylPhe, oder 2,2-Diphenylglycin oder 3-(2-Naphthyl)-D-alanin ist,

C_1 gegebenenfalls in Stellung 5 oder 6 durch Halogen, NO_2 oder C_{1-3}Alkoxy und/oder in Stellung 1 durch Formyl oder Acetyl substituiertes D-Trp, 3-(2- or 1-(Naphthyl)-D-Alanin, 3-D-Pyridylalanin, D-Tyr, gegebenenfalls durch Halogen, C_{1-3}Alkyl und/oder C_{1-3}Alkoxy substituiertes DPhe, oder P-3-Pz-Ala, D-Tin-Glu oder D-Nic-Lys ist,

D_1 is L-Ser bedeutet,

E_1 Tyr, Phe wobei der Phenylring gegebenenfalls durch Halogen, C_{1-3}Alkyl und/oder C_{1-3}Alkoxy substituiert ist, Orn, Lys, Lys-Nic, MPic-Lys, Lys-Pic, DMG-Lys, Pmc-Lys, Pzc-Lys, His, Dpo, Arg, 3-(3-Pyridyl)-Ala, Trp, N-(3-Pyridyl)acetyl-Lys oder Glu(pMeO-phenyl), Cit, HOBLys oder PzACAla bedeutet,

F_1 D-Phe, wobei der Phenylring gegebenenfalls durch Halogen, NO_2, C_{1-3}Alkyl oder C_{1-3}Alkoxy substituiert ist, gegebenenfalls in Stellung 5 oder 6 durch Halogen, NO_2 und/oder C_{1-3}Alkoxy und/oder in Stellung 1 durch Formyl oder Acetyl substituiertes D-Trp, 3-(2-Naphthyl)-L-alanyl, D-Tyr, D-Orn, D-Lys, D-Lys-Nic, D-MNic-Lys, D-MPic-Lys, D-Pmc-Lys, D-Pzc-Lys, D-Bz-Lys, D-ILys, AnGlu, D-NACAla, D-PzACAla, D-PmACAla, D-3-(3-Pyridyl)-Ala, D-His (H oder Benzyl subst.), D-Arg, D-homo-Arg(Et_2), D-Cit, D-HCit, D-Lys-Pic, D-Cit(C_{1-3}Alkyl), D-HCit(C_{1-3}alkyl), D-Glu(AA) oder α-Amino-ω -ureido-C_{2-4}alkancarboxysäure ist,

G_1 Leu, Nle, Nval, N-α-MethylLeu, Trp, Phe, Met, Tyr, Val, Ile, allolle, Abu oder Ala bedeutet,

H_1 Arg, lOrn, lLys oder Cyp-Lys bedeutet

I_1 Pro, Hydroxyprolin, 3,4-Dehydroprolin, Pip ist und

K_1 D-Ala, D-Leu, Gly, D-Ser oder Sar bedeutet,

in freier Form oder in Salzform.

6. Verfahren nach Anspruch 1 zur Herstellung eines Liganden wobei das Peptid ein Bombesin-Antagonist der Formel IXa ist

$$R_{36} - A_6 - B_3 - C_3 - D_3 - E_3 - F_3 - G_3 - H_3 - I_3 - Q \quad \text{(IXa)}$$
$$\quad\quad 1 \quad\quad 2 \quad\quad 3 \quad\quad 4 \quad\quad 5 \quad\quad 6 \quad\quad 7 \quad\quad 8 \quad\quad 9 \quad\quad 10$$

worin

- R_{36} Wasserstoff, C_{1-6}Alkyl, C_{2-6}Alkanoyl, C_{4-6}Cycloalkoxycarbonyl oder C_{1-4}Alkoxycarbonyl bedeutet,
- A_6 eine direkte Bindung oder Gly, Arg, Lys, Phe, Asp, Nal, Pro, β-Ala oder Glp ist,
- B_3 eine direkte Bindung oder Gly, Pro oder Asn ist,
- C_3 eine direkte Bindung oder Lys oder D-Nal bedeutet,
- D_3 eine direkte Bindung oder His, MeHis, EtHis, PrHis, Gln, Glu (OMe)-Glp, Leu, MeLeu, Lys, Pal, Phe, Pro, Arg, Trp oder Thr ist,
- E_3 Trp, Val, Nal, Leu, Lys, Pal bedeutet,
- F_3 Ala, MeAla, Aib, Gly, Pro, Leu, Phe, Ser, Val, Nal, Thr, Arg oder Glu ist,
- G_3 Val, Aib, Leu, Ile, Thr, Phe oder Ser ist,
- H_3 Gly, Sar, Ala, Ser, Aib, Pro, Lys, Asp, Arg, Val, Ac^3c, Ac^5c oder Ac^6c ist,
- I_3 His, MeHis, Aib, Val, Leu, MeLeu, Ala, Ile, Met, Pro, Phe, Gln, Lys, Pal, Ser, Thr, Glu, Asp, Trp oder Nal bedeutet, und
- Q K_3-R_{37} bedeutet, worin K_3 Leu, MeLeu, Ile, MeIle, Aib, Pro, Val, MeVal, Phe, Ape, MeApe, Met, Ser, Gln, Glu oder Trp und R_{37} is C_{1-3}Alkylamino, C_{1-4}(Dialkyl)amino or C_{1-3}Alkoxy ist oder Q C_{1-6}Alkoxy, C_{1-10}Alkylamino oder C_{1-10}(Dialkyl)amino ist,

oder eine Verbindung der Formel IXb ist

$$A_7 - B_4 - Gln - Trp - Ala - Val - W - X_6 - Y_6 - T_1 \quad \text{(IXb)}$$
$$1 \quad 2 \quad 3 \quad 4 \quad 5 \quad 6 \quad 7 \quad 8 \quad 9 \quad 10$$

worin

- A_7 Wasserstoff, Boc, Lys, Arg ist,
- B_4 eine direkte Bindung oder Asn, Thr, Glp ist,
- W Gly oder Ala bedeutet,
- X_6 eine direkte Bindung, His(R_{38}), Phe, Ser oder Ala ist,
- Y_6 eine direkte Bindung, Leu oder Phe ist,
- T_1 Amino, $NH(CH_2)_4CH_3$, Benzylamino, Met-R_{39}, Leu-R_{39}, Ile-R_{39}, oder Nle-R_{39} bedeutet,
- R_{38} Wasserstoff oder Benzyl ist, und
- R_{39} Amino, Hydroxy, Methoxy oder -$NHNH_2$ bedeutet,

in freier Form oder in Salzform.

7. Verfahren nach Anspruch 1 zur Herstellung eines Liganden, der

DTPA-β-Ala-mEGF, [DTPA-β-Ala-Trp^{14}]tetragastrin, Acetyl-DPhe(pCl)-DPhe(pCl)-DTrp-Ser-Tyr-DLys(DTPA)-Leu-Arg-Pro-DAla-NH_2, DTPA-DNal-$(2)^1$-DPhe-(p-Cl)-DTrp-Ser-Tyr-DLys(CH_2-CHOH-CH_2OH)-Leu-Lys-CH_2-CHOH-CH_2OH)-Pro-DAla-NH_2 und Acetyl-His-Trp-Ala-Val-DAla-Lys(β-Ala-DTPA)-Leu-OEt ist.

8. Verfahren nach einem der vorstehenden Ansprüche, wobei der Ligand mit einer Verbindung, die ein nachweisbares Element ergibt, als weitere Verfahrensstufe komplexiert wird.

9. Verfahren nach Anspruch 8, wobei es sich bei dem nachweisbaren Element um ein fluoreszierendes, α-, β- oder γ-emittierendes Element handelt.

10. Verfahren nach einem der vorstehenden Ansprüche, wobei die hergestellte Verbindung mit einem pharmazeutisch verträglichen Trägerstoff oder Verdünnungsmittel gemischt wird.

11. Verwendung eines Liganden hergestellt nach Anspruch 8 oder 9 zur Herstellung eines Abbildungsmittels wenn das nachweisbare Element ein fluoreszierendes oder γ-emittierendes Element ist, oder zur Herstellung eines therapeutischen Mittels wenn das nachweisbare Element ein α- oder β-emittierendes Element ist.

12. Verfahren zur Herstellung einer Verbindung der Formel XII

$$A\text{-}Z'_1\text{-}CO\text{-}X_7 \qquad (XII)$$

worin

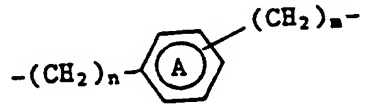
A eine Polyaminopolyessigsäure chelatbildende Gruppe ist,

Z'_1 entweder eine direkte Bindung oder -Z-R-, worin Z NH oder CO ist, bedeutet, und

R C_{1-11}Alkylen, Hydroxy-substituiertes C_{2-11}Alkylen, C_{2-11}Alkenylen,

$$-CH-,$$
$$|$$
$$R_5$$

Cyclohexylen, substituiertes Cyclohexylen, oder ein Rest der Formel (α_2)



(α_2)

worin n und m unabhängig voneinander 0, 1, 2 or 3 bedeuten,
der Ring A substituiert oder unsubstituiert ist, und

R_5 den an Cα gebundenen Rest einer natürlichen oder synthetischen Aminosäure bedeutet, und

X_7 -NH-NH_2 in geschützter oder ungeschützter Form oder -N_3 bedeutet, ist,

wobei das Verfahren die Umsetzung einer Verbindung der Formel XI

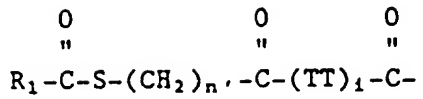
$$A - Z - R - Z_2 \qquad (XI)$$

worin A und R wie oben angegeben sind, Z für CO oder NH und Z_2 für COOH oder einen reaktiven COOH tragenden Chelator oder einen funktionellen Derivat davon steht, mit Hydrazin oder einem Derivat davon, und dann die Umsetzung der erhaltenen Verbindung in ein Azid, umfasst.

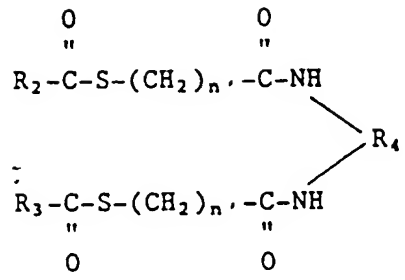
Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Un ligand comprenant un pèptide biologiquement actif choisi dans le groupe constitué par les facteurs de croissance, l'insuline, la LHRH, la gastrine, le peptide de libération de la gastrine, l'hormone de libération de la thyréostimuline, la thyréostimuline, la prolactine, le peptide intestinal vaso-actif, l'angiotensine, les interférons, la IL-1, la IL-4 et la IL-6, et leurs analogues ou dérivés, et comportant au moins un groupe de chélation choisi parmi les groupes polyamino-polycarboxyliques, les groupes de formule IIa et IIb



(IIa)

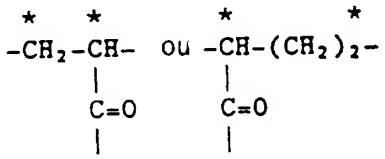


(IIb)

où

chaque R_1, R_2 et R_3 signifie indépendamment un groupe alkyle en C_1-C_6, aryle en C_6-C_8 ou arylalkyle en C_7-C_9, chacun éventuellement substitué par un groupe OH, alcoxy en C_1-C_4, COOH ou SO_3H,

R_4 signifie



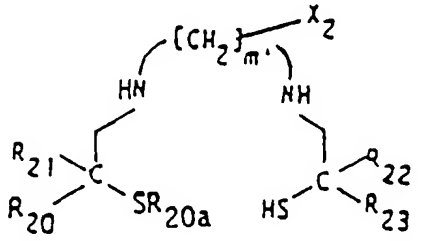
où les atomes de carbone marqués d'un astérisque sont fixés aux groupes imino,

n' signifie 1 ou 2,

i signifie un nombre entier de 2 à 6, et

TT signifient indépendamment des α- ou β-amino-acides fixés l'un à l'autre par des liaisons amide,

et les groupes dérivés des composés de formule III



(III)

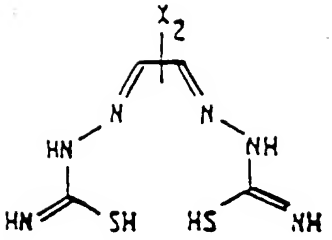
où

chaque R_{20}, R_{20a}, R_{21}, R_{22} et R_{23} signifie indépendamment l'hydrogène ou un groupe alkyle en C_1-C_4,

X_2 signifie un groupe pouvant réagir avec le groupe N-amino du peptide, ou un groupe capable de liaison avec un groupe divalent formant pont, et

m' signifie 2 ou 3,

les groupes dérivés des composés de formule IV

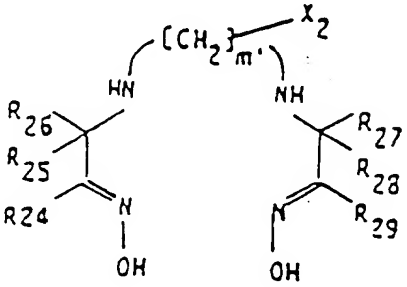


(IV)

où

X_2 est tel que défini ci-dessus,

les groupes dérivés des composés de formule V



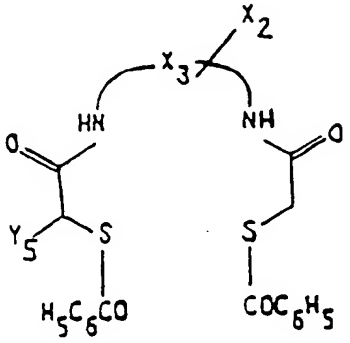
(V)

où

chaque R_{24}, R_{25}, R_{26}, R_{27}, R_{28} et R_{29} signifie indépendamment l'hydrogène ou un groupe alkyle en C_1-C_4, et

X_2 et m' sont tels que définis plus haut,

les groupes dérivés des composés de formule VI



(VI)

où

X_2 est tel que défini plus haut,

X_3 signifie un groupe alkylène en C_1-C_4, un groupe alkylène en C_1-C_4 substitué par un ou deux groupes CO_2R_{30}, CH_2COR_{30}, $CONH_2$ ou $CONHCH_2CO_2R_{30}$,un groupe phénylène ou un groupe phénylène substitué par CO_2R_{30} où R_{30} signifie un groupe alkyle en C_1-C_4, et

Y_5 signifie l'hydrogène ou CO_2R_{30},

et les groupes dérivés des porphyrines ou du Desferal,

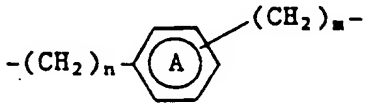
le groupe de chélation étant fixé directement ou indirectement à l'aide d'un groupe divalent formant pont à un groupe amino dudit peptide de telle sorte à former une liaison amide, le groupe divalent formant pont étant un groupe de formule α_1

Z-R-CO- (α_1)

où

R signifie un groupe alkylène en C_1-C_{11}, alkylène en C_2-C_{11} hydroxy-substitué, alcénylène en C_2-C_{11},

cyclohexylène, cyclohexylène substitué ou un radical de formule (α_2)



(α_2)

où n et m sont tels que définis plus haut, le cycle A est substitué ou non substitué, et

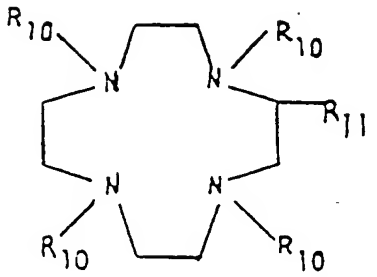
R_5 signifie un reste tel que fixé en Cα d'un α-amino-acide naturel ou synthétique, et

Z signifie NH ou CO, ledit groupe amino du peptide n'étant pas fixé directement à un reste aromatique,

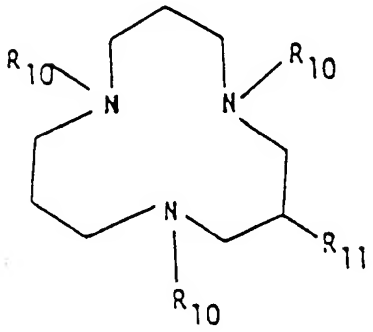
le groupe de chélation étant capable de complexer un élément décelable et le groupe amino dudit peptide n'ayant pas d'affinité de liaison importante aux récepteurs cibles, le groupe de chélation devant être autre que l'EDTA ou l' EDTA substitué lorsque le peptide est l'insuline, sous forme libre ou sous forme d'un sel.

2. Un ligand selon la revendication 1, caractérisé en ce que le groupe de chélation est un groupe polyamino-poly(acide acétique) choisi dans le groupe dérivé de l'acide diéthylène-triamine-pentaacétique (DTPA), de l'acide N-hydroxyéthyl-N,N',N'-éthylène-diaminetriacétique (HEDTA), de l' acide éthylèneglycol-O,O'-bis(2-aminoéthyl)-N,N,N',N'-tétraacétique (EGTA), de l'acide N,N'-bis(hydroxybenzyl)-éthylène-diamine-N,N'-diacétique (HBED), de l'acide triéthylènetétramine-hexaacétique (TTHA), de l'EDTA ou du DTPA substitué, de l'acide 1,4,7,10-tétraazacyclododécane-N,N',N''N'''-tétraacétique (DOTA), de l'acide 1,4,8,11-tétraazacyclotétradécane-N,N',N'',N'''-tétraacétique (TETA), le groupe de chélation étant autre que l'EDTA substitué lorsque le peptide est l'insuline.

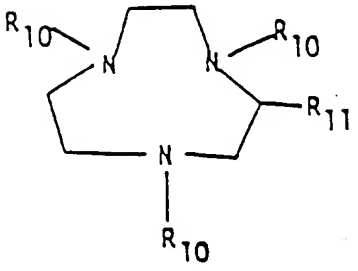
3. Un ligand comprenant un peptide biologiquement actif choisi dans le groupe constitué par les facteurs de croissance, l'insuline, la LHRH, la gastrine, le peptide de libération de la gastrine, l'hormone de libération de la thyréostimuline, la thyréostimuline, la prolactine, le peptide intestinal vaso-actif, l'angiotensine, les interférons, la IL-1, la IL-4 et la IL-6, et leurs analogues ou dérivés, et comportant au moins un groupe de chélation dérivé de l'acide H'-p-isothiocyanatobenzyl-diéthylène-triamine-N,N,N'',N''-tétraacétique, de l'acide N'-p-isothiocyanatophénéthyl-diéthylène-triamine-N,N,N'',N''-tétraacétique, de la N-{2-[bis(carboxyméthyl)amino]éthyl}-N'-{2-[bis(carboxyméthyl)amino]-2-(p-isothiocyanatobenzyl)-éthyl}-glycine, d'un composé de formule Ia, Ib ou Ic



(Ia)



(Ib)

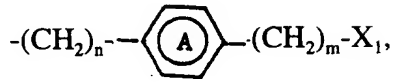


(Ic)

où

R_{10} signifie $-CH_2COOH$ ou l'un de ses dérivés fonctionnels, et

R_{11} signifie -Alk-X_1 ou



où chaque n et m signifie indépendamment 0, 1, 2 ou 3, Alk signifie un groupe alkylène en C_1-C_{11}, X_1 signifie -NCS ou NH_2 éventuellement substitué par un groupe protecteur et le cycle A est substitué ou non substitué,

ou dérivé d'un composé de formule III à VI tel que défini à la revendication 1, dans lequel X_2 signifie $-(X_4)_{n''}-X_5$ où X_4 signifie un groupe alkylène en C_1-C_6; un groupe alkylène en C_1-C_6 éventuellement fixé à l'atome de carbone par un atome d'oxygène ou -NH- ou phényl-alkyle en C_1-C_3; n" signifie 0 ou 1 et X_5 signifie -NCS,-NCO ou un groupe carboxy ou l'un de ses dérivés fonctionnels.

4. Un ligand selon l'une quelconque des revendications 1, 2 ou 3, dans lequel le facteur de croissance est l'EGF, l'IGF, le facteur de croissance des fibroblastes, le facteur de nécrose tumorale, le facteur de croissance induisant la transformation, le facteur de croissance dérivé des plaquettes, le facteur de

croissance des cellules nerveuses, la LHRH ou la bombésine, ou un analogue ou un dérivé de ces composés, ou un agoniste de la LHRH ou un antagoniste de la LHRH.

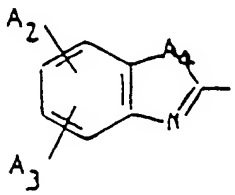
5. Un ligand selon l'une quelconque des revendications précédentes, dans lequel le peptide est un antagoniste de la LHRH de formule VII

R_{33} - A_1 - B_1 - C_1 - D_1 - E_1 - F_1 - G_1 - H_1 - I_1 - K_1 - NH_2 (VII)

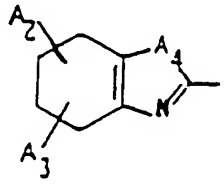
où

R_{33} signifie l'hydrogène ou un groupe acyle en C_1-C_7 ou carbamoyle,

A_1 signifie D-Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe CF_3, alkyle en C_1-C_3 et/ou alcoxy en C_1-C_3, α- ou β-naphtyl-D-alanine, D-Trp éventuellement substitué en position 5 ou 6 par un halogène ou par un groupe alcoxy en C_1-C_3 et/ou en position 1 par un groupe formyle ou acétyle, D- ou L- Pro, D- ou L-3,4-déhydroproline, D- ou L-Ser, D- ou L-Thr, D- ou L-Ala, D-pyroglutamine, 3-(9-anthryl)-D,L-alanyle, 3-(2-fluorényl)-D,L-alanyle ou 3-(Het)-D,L-alanyle où Het signifie un radical aryle hétérocyclique choisi parmi



et



où

A_2 et A_3 sont choisis indépendamment dans le groupe constitué par l'hydrogène, le chlore, le brome et les groupes alkyle en C_1-C_4, et

A_4 signifie O, S ou N,

B_1 signifie D-Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe NO_2, alkyle en C_1-C_3 ou alcoxy en C_1-C_3, D-α-méthylPhe éventuellement substitué en position 4 par du chlore, 2,2-diphénylglycine ou 3-(2-naphtyl)-D-alanine,

C_1 signifie D-Trp éventuellement substitué en position 5 ou 6 par de l'halogène ou par un groupe NO_2 ou alcoxy en C_1-C_3 et/ou en position 1 par un groupe formyle ou acétyle, 3-(2- ou 1-(naphtyl)-D-alanine, 3-D-pyridylalanine, D-Tyr, D-Phe éventuellement substitué par de l'halogène ou par un groupe alkyle en C_1-C_3 et/ou alcoxy en C_1-C_3, D-3-Pz-Ala, D-Tin-Glu ou D-Nic-Lys,

D_1 signifie L-Ser,

E_1 signifie Tyr, Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe alkyle en C_1-C_3 et/ou alcoxy en C_1-C_3, Orn, Lys, Lys-Nic, MPic-Lys, Pic-Lys, DPic-Lys, Mpic-Lys, DMG-Lys, Pmc-Lys, Pzc-Lys, PmACAla, PzACAla, His, Dpo, Arg, 3-(3-pyridyl)-Ala, Trp, N-(3-pyridyl)acétyl-Lys ou Glu(pMeO-phényle), Cit, HOBLys ou PzACAla,

F_1 signifie D-Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe NO_2, NH_2, alkyle en C_1-C_3 ou alcoxy en C_1-C_3,D-Trp éventuellement substitué en position 5 ou 6 par un halogène ou par un groupe NO_2 et/ou alcoxy en C_1-C_3 et/ou en position 1 par un groupe formyle ou acétyle, 3-(2-naphtyl)-L-alanyle, D-Tyr, D-Orn, D-Lys, D-Lys-Nic, D-MNic-Lys, D-MPic-Lys, Pic-Lys, DPic-Lys, D-Pmc-Lys, D-Pzc-Lys. D-Bz-Lys, D-ILys, AnGlu, D-NACAla, D-PzACAla, D-PmACAla, D-3-(3-pyridyl)-Ala, D-His (substitué par H ou par un groupe benzyle), D-Arg, D-homo-Arg(Et_2), D-Cit, D-HCit, D-Lys-Pic, D-Cit(alkyle en C_1-C_3), D-HCit(alkyle en C_1-C_3), D-Glu(AA) ou un acide α-amino-ω-uréido-alcanoïque en C_2-C_4,

G_1 signifie Leu, Nle, Nval, N-α-méthylLeu, Trp, Phe, Met, Tyr, Val, Ile, alloIle, Abu ou Ala,

H_1 signifie Arg, lOrn, Lys, lLys ou Cyp-Lys,

I_1 signifie Pro, hydroxyproline, 3,4-déhydroproline, Pip, et

K_1 signifie D-Ala, D-Leu, Gly, Ser ou Sar,

sous forme libre ou sous forme d'un sel.

6. Un ligand selon l'une quelconque des revendications précédentes, dans lequel le peptide est un antagoniste de la bombésine de formule IXa

$$\underset{}{R_{36}} - \underset{1}{A_6} - \underset{2}{B_3} - \underset{3}{C_3} - \underset{4}{D_3} - \underset{5}{E_3} - \underset{6}{F_3} - \underset{7}{G_3} - \underset{8}{H_3} - \underset{9}{I_3} - \underset{10}{Q} \quad \text{(IXa)}$$

où

- R_{36} signifie l'hydrogène ou un groupe alkyle en C_1-C_6, alcanoyle en C_2-C_6, (cycloalcoxy en C_4-C_6)-carbonyle ou (alcoxy en C_1-C_4)-carbonyle,
- A_6 signifie une liaison directe, Gly, Arg, Lys, Phe, Asp, Nal, Pro, β-Ala ou Glp,
- B_3 signifie une liaison directe, Gly, Pro ou Asn,
- C_3 signifie une liaison directe, Lys ou D-Nal,
- D_3 signifie une liaison directe, His, MeHis, EtHis, PrHis, Gln, Glu, (OMe)-Glp, Leu, MeLeu, Lys, Pal, Phe, Pro, Arg, Trp ou Thr,
- E_3 signifie Trp, Val, Nal, Leu, Lys ou Pal,
- F_3 signifie Ala, MeAla, Aib, Gly, Pro, Leu, Phe, Ser, Val, Nal, Thr, Arg ou Glu,
- G_3 signifie Val, Aib, Leu, Ile, Thr, Phe ou Ser,
- H_3 signifie Gly, Sar, Ala, Ser, Aib, Pro, Lys, Asp, Arg, Val, Ac^3c, Ac^5c ou Ac^6c,
- I_3 signifie His, MeHis, Aib, Val, Leu, MeLeu, Ala, Ile, Met, Pro, Phe, Gln, Lys, Pal, Ser, Thr, Glu, Asp, Trp ou Nal, et
- Q signifie K_3-R_{37} où K_3 signifie Leu, MeLeu, Ile, MeIle, Aib, Pro, Val, MeVal, Phe, Ape, MeApe, Met, Ser, Gln, Glu ou Trp et R_{37} signifie un groupe alkylamino en C_1-C_3, (dialkyl en C_1-C_4)-amino ou alcoxy en C_1-C_3 ou bien Q signifie un groupe alcoxy en C_1-C_6, alkylamino en C_1-C_{10} ou (dialkyl en C_1-C_{10})amino,

ou un composé de formule IXb

$$\underset{1}{A_7} - \underset{2}{B_4} - \underset{3}{Gln} - \underset{4}{Trp} - \underset{5}{Ala} - \underset{6}{Val} - \underset{7}{W} - \underset{8}{X_6} - \underset{9}{Y_6} - \underset{10}{T_1} \quad \text{(IXb)}$$

où

- A_7 signifie l'hydrogène, Boc, Lys ou Arg,
- B_4 signifie une liaison directe, Asn, Thr ou Glp,
- W signifie Gly ou Ala,
- X_6 signifie une liaison directe, His(R_{38}), Phe, Ser ou Ala,
- Y_6 signifie une liaison directe, Leu ou Phe,
- T_1 signifie un groupe amino, $NH(CH_2)_4CH_3$, benzylamino, Met-R_{39}, Leu-R_{39}, Ile-R_{39} ou Nle-R_{39},
- R_{38} signifie l'hydrogène ou un groupe benzyle, et
- R_{39} signifie un groupe amino, hydroxy, méthoxy ou $-NHNH_2$,

sous forme libre ou sous forme d'un sel.

7. Un ligand selon l'une quelconque des revendications précédentes, dans lequel le groupe de chélation est fixé au groupe amino terminal.

8. Un ligand selon l'une quelconque des revendications précédentes, dans lequel le groupe de chélation est fixé à un groupe amino de la chaîne latérale.

9. Un ligand qui est la

DTPA-β-Ala-mEGF, la [DTPA-β-Ala-Trp^{14}]-tétragastrine, l'acétyl-DPhe(pCl)-DPhe(p-Cl)-DTrp-Ser-Tyr-DLys(DTPA)-Leu-Arg-Pro-DAla-NH_2, le DTPA-DNal-(2)^1-DPhe(p-Cl)-DTrp-Ser-Tyr-DLys(CH_2-CHOH-CH_2OH)-Leu-Lys(CH_2-CHOH-CH_2OH)-Pro-DAla-NH_2 et l'acétyl-His-Trp-Ala-Val-DAla-Lys(β-Ala-DTPA)-Leu-OEt.

10. Un procédé de préparation d'un ligand selon la revendication 1 ou 3, comprenant
a) l'élimination d'au moins un groupe protecteur qui est présent dans un peptide comportant un groupe de chélation, ou
b) le couplage par une liaison amide de deux fragments peptidiques, chacun d'eux contenant au moins un amino-acide sous forme protégée ou non protégée et l'un d'entre eux contenant le groupe de chélation, la liaison amide étant de telle sorte qu'on obtient la séquence d'amino-acides désirée, et ensuite éventuellement la mise en oeuvre de l'étape a) du procédé, ou
c) le couplage d'un agent de chélation et du peptide désiré sous forme protégée ou non protégée, de telle sorte que le groupe de chélation soit fixé au groupe amino désiré du peptide, et ensuite éventuellement la mise en oeuvre de l'étape a) du procédé, ou
d) l'élimination d'un groupe fonctionnel d'un peptide non protégé ou protégé comportant un groupe de chélation ou sa transformation en un autre groupe fonctionnel, afin d'obtenir un autre peptide non protégé ou protégé comportant un groupe de chélation et, dans ce dernier cas, la mise en oeuvre de l'étape a) du procédé,
et la récupération du ligand ainsi obtenu sous forme libre ou sous forme d'un sel.

11. Une composition pharmaceutique comprenant un ligand selon l'une quelconque des revendications 1 à 9, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, en association avec un véhicule ou diluant pharmaceutiquement acceptable.

12. Un ligand tel que défini à l'une quelconque des revendications 1 à 9, complexé avec un élément décelable, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable.

13. Un ligand selon la revendication 12, dans lequel l'élément décelable est un élément fluorescent ou à émission de rayons α, β ou γ.

14. Un ligand selon la revendication 12, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, pour l'utilisation comme médicament.

15. Un ligand selon la revendication 12, sous forme libre, pour l'utilisation comme agent d'imagerie lorsque l'élément décelable est un élément fluorescent ou à émission de rayons γ, ou pour l'utilisation en thérapeutique lorsque l'élément décelable est un élément à émission de rayons α ou β.

16. Une composition pharmaceutique comprenant un ligand selon la revendication 12, sous forme libre ou sous forme d'un sel pharmaceutiquement acceptable, en association avec un véhicule ou diluant pharmaceutiquement acceptable.

17. Un procédé de préparation d'un ligand selon la revendication 12, comprenant la complexation d'un ligand selon l'une quelconque des revendications 1 à 9, sous forme libre ou sous forme d'un sel, avec un composé fournissant un élément décelable.

18. Un composé de formule XII

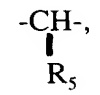
$A\text{-}Z'_1\text{-}CO\text{-}X_7$ (XII)

où

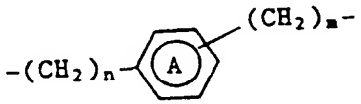
A signifie un groupe de chélation polyamino-poly(acide acétique),

Z'_1 signifie une liaison directe ou -Z-R où Z signifie NH ou CO, et

R signifie un groupe alkylène en C_1-C_{11}, alkylène en C_2-C_{11} hydroxy substitué, alcénylène en C_2-C_{11},



cyclohexylène, cyclohexylène substitué ou un radical de formule (α_2)



(α_2)

où

chaque n et m signifie indépendamment 0, 1, 2 ou 3, le cycle A étant substitué ou non substitué, et

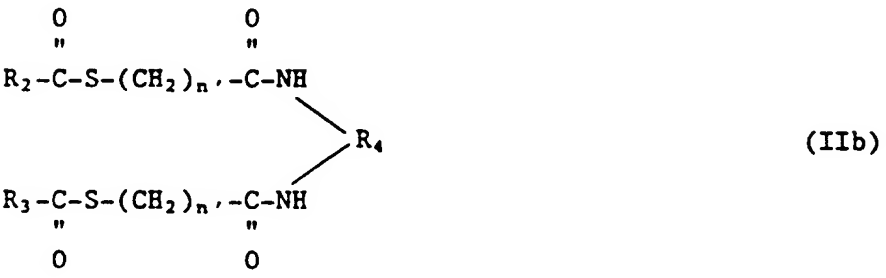
R_5 signifie un reste tel que fixé en Cα d'un α-amino-acide naturel ou synthétique, et

X_7 signifie -NH-NH_2 sous forme protégée ou non protégée ou -N_3.

Revendications pour l'Etat contractant suivant : ES

1. Un procédé de prépration d'un ligand comprenant un peptide biologiquement actif choisi dans le groupe constitué par les facteurs de croissance, l'insuline, la LHRH, la gastrine, le peptide de libération de la gastrine, l'hormone de libération de la thyréostimuline, la thyréostimuline, la prolactine, le peptide intestinal vaso-actif, l'angiotensine, les interférons, la IL-1, la IL-4 et la IL-6, et leurs analogues ou dérivés, et comportant au moins un groupe de chélation choisi parmi les groupes polyamino-polycarboxyliques, les groupes de formule IIa et IIb

(IIa)

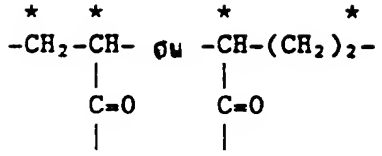


(IIb)

où

chaque R_1, R_2 et R_3 signifie indépendamment un groupe alkyle en C_1-C_6, aryle en C_6-C_8 ou arylalkyle en C_7-C_9, chacun éventuellement substitué par un groupe OH, alcoxy en C_1-C_4, COOH ou SO_3H,

R_4 signifie



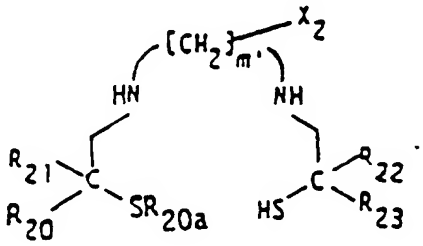
où les atomes de carbone marqués d'un astérisque sont fixés aux groupes imino,

n' signifie 1 ou 2,

i signifie un nombre entier de 2 à 6, et

TT signifient indépendamment des α- ou β-amino-acides fixés l'un à l'autre par des liaisons amide,

et les groupes dérivés des composés de formule III



(III)

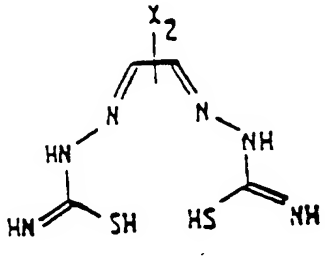
où

chaque R_{20}, R_{20a}, R_{21}, R_{22} et R_{23} signifie indépendamment l'hydrogène ou un groupe alkyle en C_1-C_4,

X_2 signifie un groupe pouvant réagir avec le groupe N-amino du peptide, ou un groupe capable de liaison avec un groupe divalent formant pont, et

m' signifie 2 ou 3,

les groupes dérivés des composés de formule IV

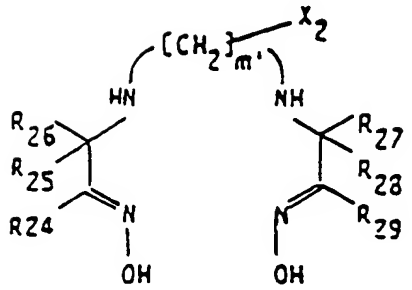


(IV)

où

X_2 est tel que défini ci-dessus,

les groupes dérivés des composés de formule V



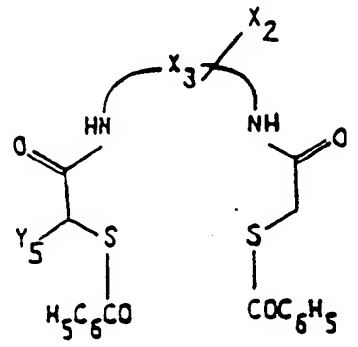
(V)

où

chaque R_{24}, R_{25}, R_{26}, R_{27}, R_{28} et R_{29} signifie indépendamment l'hydrogène ou un groupe alkyle en C_1-C_4, et

X_2 et m' sont tels que définis plus haut,

les groupes dérivés des composés de formule VI



(VI)

où

X_2 est tel que défini plus haut,

X_3 signifie un groupe alkylène en C_1-C_4, un groupe alkylène en C_1-C_4 substitué par un ou deux groupes CO_2R_{30}, CH_2COR_{30}, $CONH_2$ ou $CONHCH_2CO_2R_{30}$,un groupe phénylène ou un groupe phénylène substitué par CO_2R_{30} où R_{30} signifie un groupe alkyle en C_1-C_4, et

Y_5 signifie l'hydrogène ou CO_2R_{30},

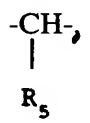
et les groupes dérivés des porphyrines ou du Desferal,

le groupe de chélation étant fixé directement ou indirectement à l'aide d'un groupe divalent formant pont à un groupe amino dudit peptide de telle sorte à former une liaison amide, le groupe divalent formant pont étant un groupe de formule α_1

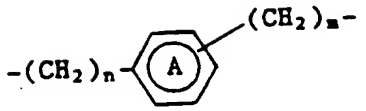
Z-R-CO- (α_1)

où

R signifie un groupe alkylène en C_1-C_{11}, alkylène en C_2-C_{11} hydroxy substitué, alcénylène en C_2-C_{11},



cyclohexylène, cyclohexylène substitué ou un radical de formule (α_2)



(α_2)

où n et m sont tels que définis plus haut, le cycle A est substitué ou non substitué, et

R_5 signifie un reste tel que fixé en Cα d'un α-amino-acide naturel ou synthétique, et

Z signifie NH ou CO, ledit groupe amino du peptide n'étant pas fixé directement à un reste aromatique, le groupe de chélation étant capable de complexer un élément décelable et le groupe amino dudit peptide n'ayant pas d'affinité de liaison importante aux récepteurs cibles, le groupe de chélation devant être autre que l'EDTA ou l'EDTA substitué lorsque le peptide est l'insuline, sous forme libre ou sous forme d'un sel,

lequel procédé comprend

a) l'élimination d'au moins un groupe protecteur qui est présent dans un peptide comportant un groupe de chélation, ou

b) le couplage par une liaison amide de deux fragments peptidiques, chacun d'eux contenant au moins un amino-acide sous forme protégée ou non protégée et l'un d'entre eux contenant le groupe de chélation, la liaison amide étant de telle sorte qu'on obtient la séquence d'amino-acides désirée, et ensuite éventuellement la mise en oeuvre de l'étape a) du procédé, ou

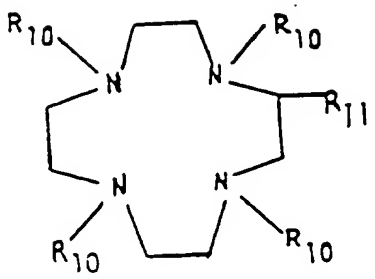
c) le couplage d'un agent de chélation et du peptide désiré sous forme protégée ou non protégée, de telle sorte que le groupe de chélation soit fixé au groupe amino désiré du peptide, et ensuite éventuellement la mise en oeuvre de l'étape a) du procédé, ou

d) l'élimination d'un groupe fonctionnel d'un peptide non protégé ou protégé comportant un groupe de chélation ou sa transformation en un autre groupe fonctionnel, afin d'obtenir un autre peptide non protégé ou protégé comportant un groupe de chélation et, dans ce dernier cas, la mise en oeuvre de l'étape a) du procédé,

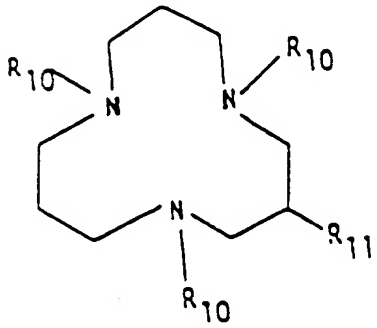
et la récupération du ligand ainsi obtenu sous forme libre ou sous forme d'un sel.

2. Un procédé selon la revendication 1 pour la préparation d'un ligand dans lequel le groupe de chélation est un groupe polyamino-poly(acide acétique) choisi dans le groupe dérivé de l'acide diéthylène-triamine-pentaacétique (DTPA), de l'acide N-hydroxyéthyl-N,N',N'-éthylène-diaminetriacétique (HEDTA), de l'acide éthylèneglycol-O,O'-bis(2-aminoéthyl)-N,N,N',N'-tétraacétique (EGTA), de l'acide N,N'-bis(hydroxybenzyl)-éthylène-diamine-N,N'-diacétique (HBED), de l'acide triéthylènetétramine-hexaacétique (TTHA), de l'EDTA ou du DTPA substitué, de l'acide 1,4,7,10-tétraazacyclododécane-N,N',N''N'''-tétraacétique (DOTA), de l'acide 1,4,8,11-tétraazacyclotétradécane-N,N',N'',N'''-tétraacétique (TETA), le groupe de chélation devant être autre que l'EDTA substitué lorsque le peptide est l'insuline.

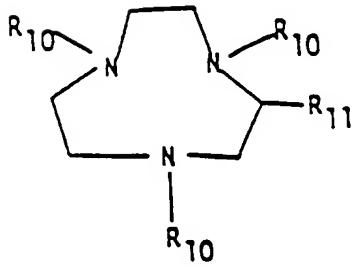
3. Un procédé selon la revendication 1 pour la préparation d'un ligand comprenant un peptide biologiquement actif choisi dans le groupe constitué par les facteurs de croissance, l'insuline, la LHRH, la gastrine, le peptide de libération de la gastrine, l'hormone de libération de la thyréostimuline, la thyréostimuline, la prolactine, le peptide intestinal vaso-actif, l'angiotensine, les interférons, la IL-1, la IL-4 et la IL-6, et leurs analogues ou dérivés, et comportant au moins un groupe de chélation dérivé de l'acide N'-p-isothiocyanato-benzyl-diéthylène-triamine-N,N,N'',N''-tétraacétique, de l'acide N'-p-isothiocyanatophénéthyl-diéthylène-triamine-N,N,N'',N''-tétraacétique, de la N-{-2[bis(carboxyméthyl)-amino]-éthyl}-N'-{2-[bis(carboxyméthyl)amino]-2-(p-isothiocyanatobenzyl)-éthyl}-glycine, d'un composé de formule Ia, Ib ou Ic



(Ia)



(Ib)

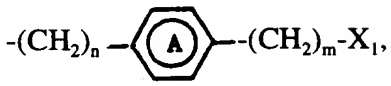


(Ic)

où

R_{10} signifie $-CH_2COOH$ ou l'un de ses dérivés fonctionnels, et

R_{11} signifie -Alk-X_1 ou



où chaque n et m signifie indépendamment 0, 1, 2 ou 3, Alk signifie un groupe alkylène en C_1-C_{11}, X_1 signifie -NCS ou NH_2 éventuellement substitué par un groupe protecteur et le cycle A est substitué ou non substitué,

ou dérivé d'un composé de formule III à VI tel que défini à la revendication 1, dans lequel X_2 signifie $-(X_4)_{n''}-X_5$ où X_4 signifie un groupe alkylène en C_1-C_6; un groupe alkylène en C_1-C_6 éventuellement fixé à l'atome de carbone par un atome d'oxygène ou -NH- ou phényl-alkyle en C_1-C_3; n'' signifie 0 ou 1 et X_5 signifie - NCS, -NCO ou un groupe carboxy ou l'un de ses dérivés fonctionnels.

4. Un procédé selon la revendication 1 pour la préparation d'un ligand dans lequel le facteur de croissance est l'EGF, l'IGF, le facteur de croissance des fibroblastes, le facteur de nécrose tumorale, le facteur de croissance induisant la transformation, le facteur de croissance dérivé des plaquettes, le

facteur de croissance des cellules nerveuses, la LHRH ou la bombésine, ou un analogue ou un dérivé de ces composés, ou un agoniste de la LHRH ou un antagoniste de la LHRH.

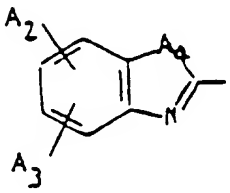
5. Un procédé selon la revendication 1 pour la préparation d'un ligand dans lequel le peptide est un antagoniste de la LHRH de formule VII

R_{33} - A_1 - B_1 - C_1 - D_1 - E_1 - F_1 - G_1 - H_1 - I_1 - K_1 - NH_2 (VII)

où

R_{33} signifie l'hydrogène ou un groupe acyle en C_1-C_7 ou carbamoyle,

A_1 signifie D-Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe CF_3, alkyle en C_1-C_3 et/ou alcoxy en C_1-C_3, α- ou β-naphtyl-D-alanine, D-Trp éventuellement substitué en position 5 ou 6 par de l'halogène ou par un groupe alcoxy en C_1-C_3 et/ou en position 1 par un groupe formyle ou acétyle, D- ou L- Pro, D- ou L-3,4-déhydroproline, D- ou L-Ser, D- ou L-Thr, D- ou L-Ala, D-pyroglutamine, 3-(9-anthryl)-D,L-alanyle, 3-(2-fluorényl)-D,L-alanyle ou 3-(Het)-D,L-alanyle où Het signifie un radical aryle hétérocyclique choisi parmi



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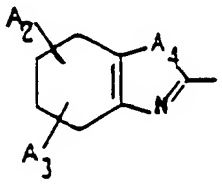


où

A_2 et A_3 sont choisis indépendamment dans le groupe constitué par l'hydrogène, le chlore, le brome et les groupes alkyle en C_1-C_4, et

A_4 signifie O, S ou N,

B_1 signifie D-Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe NO_2, alkyle en C_1-C_3 ou alcoxy en C_1-C_3, D-α-méthylPhe éventuellement substitué en position 4 par du chlore, 2,2-diphénylglycine ou 3-(2-naphtyl)-D-alanine,

C_1 signifie D-Trp éventuellement substitué en position 5 ou 6 par un halogène ou par un groupe NO_2 ou alcoxy en C_1-C_3 et/ou en position 1 par un groupe formyle ou acétyle, 3-(2- ou 1-(naphtyl)-D-alanine, 3-D-pyridylalanine, D-Tyr, D-Phe éventuellement substitué par de l'halogène ou par un groupe alkyle en C_1-C_3 et/ou alcoxy en C_1-C_3, D-3-Pz-Ala, D-Tin-Glu ou D-Nic-Lys,

D_1 signifie L-Ser,

E_1 signifie Tyr, Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe alkyle en C_1-C_3 et/ou alcoxy en C_1-C_3, Orn, Lys, Lys-Nic, MPic-Lys, Lys-Pic, Mpic-Lys, DMG-Lys, Pmc-Lys, Pzc-Lys, His, Dpo, Arg, 3-(3-pyridyl)-Ala, Trp, N-(3-pyridyl)acétyl-Lys ou Glu(pMeO-phényle), Cit, HOBLys ou PzACAla,

F_1 signifie D-Phe éventuellement substitué dans le cycle phényle par de l'halogène ou par un groupe NO_2, NH_2, alkyle en C_1-C_3 ou alcoxy en C_1-C_3,D-Trp éventuellement substitué en position 5 ou 6 par un halogène ou par un groupe NO_2 et/ou alcoxy en C_1-C_3 et/ou en position 1 par un groupe formyle ou acétyle, 3-(2-naphtyl)-L-alanyle, D-Tyr, D-Orn, D-Lys, D-Lys-Nic, D-MNic-Lys, D-MPic-Lys, D-Pmc-Lys, D-Pzc-Lys. D-Bz-Lys, D-ILys, AnGlu, D-NACAla, D-PzACAla, D-PmACAla, D-3-(3-pyridyl)-Ala, D-His (substitué par H ou par un groupe benzyle), D-Arg, D-homo-Arg(Et_2), D-Cit, D-HCit, D-Lys-Pic, D-Cit(alkyle en C_1-C_3), D-HCit(alkyle en C_1-C_3), D-Glu(AA) ou un acide α-amino-ω-uréido-alcanoïque en C_2-C_4,

G_1 signifie Leu, Nle, Nval, N-α-méthylLeu, Trp, Phe, Met, Tyr, Val, Ile, alloIle, Abu ou Ala,

H_1 signifie Arg, IOrn, ILys ou Cyp-Lys,

I_1 signifie Pro, hydroxyproline, 3,4-déhydroproline, Pip, et

K_1 signifie D-Ala, D-Leu, Gly, Ser ou Sar,
sous forme libre ou sous forme d'un sel.

6. Un procédé selon la revendication 1 pour la préparation d'un ligand dans lequel le peptide est un antagoniste de la bombésine de formule IXa

$$\underset{}{R_{36}} - \underset{1}{A_6} - \underset{2}{B_3} - \underset{3}{C_3} - \underset{4}{D_3} - \underset{5}{E_3} - \underset{6}{F_3} - \underset{7}{G_3} - \underset{8}{H_3} - \underset{9}{I_3} - \underset{10}{Q} \quad \text{(IXa)}$$

où

R_{36} signifie l'hydrogène ou un groupe alkyle en C_1-C_6, alcanoyle en C_2-C_6, (cycloalcoxy en C_4-C_6)-carbonyle ou (alcoxy en C_1-C_4)-carbonyle,
A_6 signifie une liaison directe, Gly, Arg, Lys, Phe, Asp, Nal, Pro, β-Ala ou Glp,
B_3 signifie une liaison directe, Gly, Pro ou Asn,
C_3 signifie une liaison directe, Lys ou D-Nal,
D_3 signifie une liaison directe, His, MeHis, EtHis, PrHis, Gln, Glu, (OMe)-Glp, Leu, MeLeu, Lys, Pal, Phe, Pro, Arg, Trp ou Thr,
E_3 signifie Trp, Val, Nal, Leu, Lys ou Pal,
F_3 signifie Ala, MeAla, Aib, Gly, Pro, Leu, Phe, Ser, Val, Nal, Thr, Arg ou Glu,
G_3 signifie Val, Aib, Leu, Ile, Thr, Phe ou Ser,
H_3 signifie Gly, Sar, Ala, Ser, Aib, Pro, Lys, Asp, Arg, Val, Ac^3c, Ac^5c ou Ac^6c,
I_3 signifie His, MeHis, Aib, Val, Leu, MeLeu, Ala, Ile, Met, Pro, Phe, Gln, Lys, Pal, Ser, Thr, Glu, Asp, Trp ou Mal, et
Q signifie K_3-R_{37} où K_3 signifie Leu, MeLeu, Ile, MeIle, Aib, Pro, Val, MeVal, Phe, Ape, MeApe, Met, Ser, Gln, Glu ou Trp et R_{37} signifie un groupe alkylamino en C_1-C_3, (dialkyl en C_1-C_4)-amino ou alcoxy en C_1-C_3 ou bien Q signifie un groupe alcoxy en C_1-C_6, alkylamino en C_1-C_{10}, ou (dialkyl en C_1-C_{10})amino,

ou un composé de formule IXb

$$\underset{1}{A_7} - \underset{2}{B_4} - \underset{3}{Gln} - \underset{4}{Trp} - \underset{5}{Ala} - \underset{6}{Val} - \underset{7}{W} - \underset{8}{X_6} - \underset{9}{Y_6} - \underset{10}{T_1} \quad \text{(IXb)}$$

où

A_7 signifie l'hydrogène, Boc, Lys ou Arg,
B_4 signifie une liaison directe, Asn, Thr ou Glp,
W signifie Gly ou Ala,
X_6 signifie une liaison directe, His(R_{38}), Phe, Ser ou Ala,
Y_6 signifie une liaison directe, Leu ou Phe,
T_1 signifie un groupe amino, $NH(CH_2)_4CH_3$, benzylamino, Met-R_{39}, Leu-R_{39}, Ile-R_{39} ou Nle-R_{39},
R_{38} signifie l'hydrogène ou un groupe benzyle, et
R_{39} signifie un groupe amino, hydroxy, méthoxy ou $-NHNH_2$,

sous forme libre ou sous forme d'un sel.

7. Un procédé selon la revendication 1 pour la préparation d'un ligand qui est la

DTPA-β-Ala-mEGF, la [DTPA-β-Ala-Trp^{14}]-tétragastrine, l'acétyl-DPhe(pCl)-DPhe(p-Cl)-DTrp-Ser-Tyr-DLys(DTPA)-Leu-Arg-Pro-DAla-NH_2, le DTPA-DNal-(2)^1-DPhe(p-Cl)-DTrp-Ser-Tyr-DLys(CH_2-CHOH-CH_2OH)-Leu-Lys(CH_2-CHOH-CH_2OH)-Pro-DAla-NH_2 et l'acétyl-His-Trp-Ala-Val-DAla-Lys(β-Ala-DTPA)-Leu-OEt.

8. Un procédé selon l'une quelconque des revendication précédentes, comprenant l'étape ultérieure de complexation du ligand avec un composé fournissant un élément décelable.

9. Un procédé selon la revendication 8, dans lequel l'élément décelable est un élément fluorescent ou à émission de rayons α, β ou γ.

10. Un procédé selon l'une quelconque des revendications précédentes, dans lequel le composé préparé est mélangé avec un véhicule ou diluant pharmaceutiquement acceptable.

11. L'utilisation d'un ligand préparé selon la revendication 8 ou 9, pour la fabrication d'un agent d'imagerie lorsque l'élément décelable est un élément fluorescent ou à émission de rayons γ, ou pour la fabrication d'un agent thérapeutique lorsque l'élément décelable est un élément à émission de rayons α ou β.

12. Un procédé de préparation d'un composé de formule (XII)

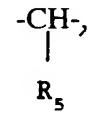
A-Z'_1-CO-X_7 (XII)

où

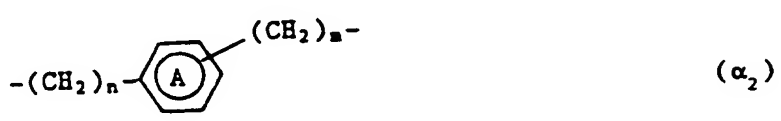
A signifie un groupe de chélation polyamino-polycarboxylique,

Z'_1 signifie une liaison directe ou -Z-R où Z signifie NH ou CO, et

R signifie un groupe alkylène en C_1-C_{11}, alkylène en C_2-C_{11} hydroxy substitué, alcénylène en C_2-C_{11},



cyclohexylène, cyclohexylène substitué ou un radical de formule (α_2)



(α_2)

où

chaque n et m signifie indépendamment 0, 1, 2 ou 3, le cycle A étant substitué ou non substitué, et

R_5 signifie un reste tel que fixé en Cα d'un α-amino-acide naturel ou synthétique, et

X_7 signifie -NH-NH_2 sous forme protégée ou non protégée ou -N_3,

comprenant la réaction d'un composé de formule XI

A - Z - R - Z_2 (XI)

où A et R sont tels que définis ci-dessus, Z signifie CO ou NH et Z_2 signifie COOH, ou d'un agent de chélation comportant un groupe -COOH réactif ou l'un de ses dérivés fonctionnels,
avec l'hydrazine ou l'un de ses dérivés, et ensuite la transformation du composé résultant en azide.